OPTIMISATION OF BIOCHEMICAL REACTORS : AN ANALYSIS OF DIFFERENT APPROXIMATIONS OF FED-BATCH OPERATION

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by

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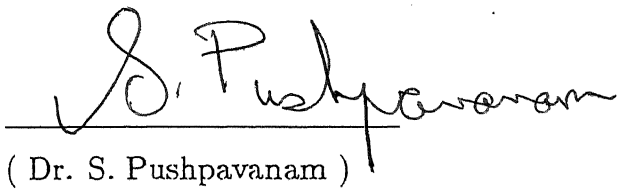
CERTIFICATE

Certified that the work contained in the thesis entitled "*Optimisation of Biochemical Reactors : An Analysis of Different Approximations of Fed-batch Operation*", by "*Pavan Kumar Shukla*", has been carried out under my supervision and that this work has not been submitted elsewhere for a degree.



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Pavan Kumar Shukla

CONTENTS

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Nomenclature

A(S): Function form of the secretion rate dependency on S.

B(S): Function form of the expression rate dependency on S.

C(S): Function form of the specific growth rate dependency on S.

F: Volumetric flow-rate (L/hr).

F_{max}: Maximum value of flow-rate.

F_{min}: Minimum value of flow-rate.

H: Hamiltonian

N: No. of stages.

n: No of repeated-fed batch cycle.

P: Cell productivity (g/hr).

P_M: Level of secreted SUC2-s2 in culture, arbitrary unit/L.

S: Substrate concentration (g/L).

S_F: Feed substrate concentration (g/L).

t: Time (hr).

t_f: Time of repeated fed-batch cycle (hr).

Δt: Duration of stage (hr).

U: Amount added in a stage (L).

U_{max}: Maximum amount added in a stage (L)

Greek

μ: Specific growth rate (hr^{-1}).

μ_{max}: Specific growth rate constant (dimensionless).

λ_X: Adjoint variable associated with X.

λ_V: Adjoint variable associated with V.

α, β, γ: Haldane kinetic parameter.

Subscripts

max: Maximum

f: Final

ABSTRACT

In this work we analyse the operation of a biochemical reactor in the repeated fed-batch mode. The reaction is assumed to follow Haldane kinetics i.e. it is characterised by substrate inhibition. The feed rate of the substrate is chosen as the control variable. The entire duration of the operation is divided into different subintervals. We optimise the system performance by approximating the feed flow-rate in a repeated fed-batch mode in two ways (i) using discrete pulses (ii) using a constant flow-rate over different sub-intervals. In the former the equations lend themselves to an analytical solution. For the second case we use a shooting method coupled with a non-linear programming technique to obtain the constant flow-rates in the different sub-intervals. This has been analysed for two scenarios (i) equal duration of sub-intervals and (ii) unequal duration of sub-intervals. The objective here is to maximise the biomass production over one cycle.

We have also studied the applicability of our method when the objective is to maximise the product formed in a non repeated fed-batch mode. The effect of converting a non-linear constraint to a linear constraint on the numerical convergence has also been investigated.

Chapter 1

INTRODUCTION

The kinetics of biochemical fermentation reactions are usually characterised by substrate inhibition and product inhibition. The fed-batch operation of such reactors results in their optimal performance. Here the substrate is added to the reactor during the course of the reaction. The biomass is usually present initially in the reactor.

The optimal operation of fermentation reactors in the fed-batch mode has been investigated by different methods. The objective here is maximising either a) the biomass production or b) the product formed. The classical methods applied have been (i) the Greens theorem, and (ii) Pontyagrin's maximum principle. Weigand (1981) considered the problem of maximising cell productivity in the repeated fed-batch mode of operation, for the case of a constant yield. He posed the problem as one where we have to minimise the time of operation. He obtained an analytical (algebraic) expression which relates the total time of operation with biomass concentration, for an optimal filling policy. No upper bound on the permissible flow-rate was assumed in the study.

San and Stephanopolous (1984) discussed the substrate feeding policy in a fed-batch reactor. They determined the solution using the maximum principle. In a later study they(San and Stephanopolous (1986)) incorporated the effect of a delay in the growth rate and determined the optimum operating conditions. Cazzador (1988) studied how the initial conditions of the reactor

determine the optimal feeding policies. These authors have investigated the operation of the reactor in a non-repeated fed-batch mode

Bonte et al(1986) and Modak, et al (1986) determined the optimal feeding policies for different kinetic models. They developed a computational scheme to obtain the feeding policy which maximised a) pencillin production b)cell mass production.

Optimal feed rate policies were determined in a non bio-chemical engineering context by other researchers. Levin (1991) discussed the problem of maximising product distribution in a batch reactor sustaining parallel reactions. The feed was added to the reactor at discrete instants of time. The equations governing the evolution of the system here are linear.

Biegler (1984) used an orthogonal collocation technique to obtain the solution to the optimal control problem. The control variable was determined using sequential quadratic programming (SQP). This method was extended to investigate systems governed by differential algebraic equations, and the case where the control profile has discontinuities (Cuthrell and Biegler (1989), Vasantarajan and Biegler,(1991)).

Morrison and Sargent (1984) have considered the optimisation problem of a multistage process, Vassliadis et al (1991) have discussed the solution method of multistage dynamic optimisation problems with path constraints. The control (usually feed-rate) profiles are allowed to be discontinuous at switching times (i.e at the junctions of different stages). These problems are solved using SQP. This method requires the derivative of the objective

function with respect to control variables. The numerical method is very sensitive to the evaluation of these derivatives. Rosen and Luus (1991) have discussed three different strategies for computing these derivatives.

In the context of biochemical engineering it has been established that the optimal policy usually consists of a singular arc (Weigand (1981), Cazzador (1988)). Here the feed rate varies continuously with time. Such a profile is usually difficult to implement experimentally. In the first part of this work we discuss the optimisation problem of maximising biomass productivity in a repeated fed-batch mode of a biochemical reactor.

The substrate feed-rate policy over one cycle is approximated as (i) discrete pulses (ii) constant feed rate over different sub intervals. The primary motivation behind this approach is it enables us to determine optimal profiles, when it is not possible to obtain these analytically by using classical techniques like maximum principle etc. These latter methods are elegant in analysing low dimensional systems.

In the second part of this work we have analysed the problem of maximising protein production in a non repeated fed-batch operation. The applicability of the method proposed for this higher dimensional system is demonstrated. The addition of the substrate using discrete pulses or constant flow-rates enables us to numerically obtain the best "practical" approximation for the theoretical optimal control policies. This approximation can be implemented experimentally.

Chapter 2

PROBLEM FORMULATION (Maximising Biomass Production)

The optimisation of the reactor in a fed batch mode consists of the following steps.

(i) At the start, the reactor volume is V_o and contains biomass of concentration X_o and substrate of concentration S_o

(ii) The substrate is added over the entire cycle of reactor operation (t_f) or till the reactor volume is filled to V_f. The reaction is allowed to proceed for t_f.

(iii) After t_f the reactor is drained and its volume reduced to V_o

(iv) The steps (ii) - (iii) are repeated for the repeated fed batch mode of operation. The non-repeated operation terminates at the end of step (ii).

The repeated fed-batch operation can be viewed as a cyclic operation of period 't_f'. The concentrations at the end of the $i^{th,}$ cycle are the initial conditions of the $(i + 1)^{th}$ cycle.

In the repeated fed-batch mode of operation we are interested only in the terminal behavior of the system. This is characterised by the state of the system after a large number of cycles. In this state the initial concentrations are identical to the terminal concentrations of a cycle. This is in contrast to the non-repeated fed-batch mode, where the terminal concentration may not be equal to the initial concentration. The most basic terminal state, will be periodic with period 't_f' and is analogous to the steady-state of a CSTR.

In each stage, the evolution of the substrate (S), biomass (X) and volume (V) is determined by the evolution equations

$$\frac{d\,(XV)}{dt} = \mu(S)\,XV \qquad (1a)$$

$$\frac{d\,(SV)}{dt} = \frac{-\,\mu(S)\,XV}{Y} + FS_F \qquad (1b)$$

$$\frac{dV}{dt} = F \qquad (1c)$$

Here $\mu(S)$ represents the dependency of the kinetics on S, Y the constant yield, S_F the feed concentration, F the feed rate of substrate.

A common assumption made in most of the earlier works is that the initial concentrations in the reactor X_o, S_o satisfy the stoichiometric relationship

$$X_o = Y\,(S_F - S_o) \qquad (2a)$$

This relationship can be used to ensure us that X, S satisfy

$$X = Y\,(S_F - S) \qquad (2b)$$

for all instants of time. This enables us to eliminate S in favour of X and reduce the order of the state equations by one. This mathematical simplification is possible only when (2a) is satisfied for the non-repeated fed-batch operation (NRFB). Here the fed-batch operation is terminated at the end of step (ii).

For the repeated fed-batch (RFB), the system evolves to a state, where the relationship (2b) is true for the N^{th} cycle, for sufficiently large N. The condition at the begining of the first cycle can hence be allowed to be non stoichiometric for this operation. We prove this in Appendix-1. For the repeated fed-batch mode of operation consequently it is not necessary to assume that the initial concentration satisfy (2a), as was assumed by Weigand (1981). The concentrations X, S in the N^{th} cycle satisfy the stoichiometric relationships (2a) for the case of repeated fed-batch operation for N sufficiently large.

Eliminating the dependency on S in the kinetic expression using (2b) we can rewrite system (1) as

$$\frac{dX}{dt} = X\,\mu(S(X)) - \frac{FX}{V} \qquad (3a)$$

$$\frac{dV}{dt} = F \qquad (3b)$$

We solve this system of equations subject to the constraints,

$$0 \le F \le F_{max}$$

and $$V_o \le V \le V_f$$

Our objective is to determine the optimal feed-rate policy F(t), which maximises the productivity over a cycle, in the terminal state of operation. This means that we want to

$$\text{Maximise } P = \frac{X_f V_f - X_o V_o}{t_f} \qquad (4a)$$

Here X_o and X_f represent biomass concentrations at the beginning and at the end of a cycle.

As discussed earlier $X_o = X_F$ in the terminal state of a repeated fed batch operation and we obtain

$$P = \frac{(V_F - V_o) X_o}{t_f} \qquad (4b)$$

where t_f is the duration of a cycle.

Weigand (1981) obtained the optimum solution by posing this problem as a minimisation of time problem for a given X_f. In this work we fix the duration of each cycle t_f, and consider the optimisation problem as one of maximising X_f. Consequently our problem is a fixed time problem.

This reduces the problem to maximising P,

$$P = X_f \qquad (4c)$$

for a fixed V_o, V_F, t_f.

Chapter 3

METHODS OF SOLUTION (MAXIMUM PRINCIPLE)

We now formulate the solution to this optimisation problem using the classical Pontyagrins maximum principle.

The Hamiltonian H for this case is defined as

$$H = \lambda_x\left[X\mu(S(X)) - \frac{F\,X}{V}\right] + \lambda_v F$$

$$=\lambda_x X\mu(S(X)) + F\left(\lambda_v - \frac{\lambda_x\, X}{V}\right) \qquad (5)$$

The evolution of the adjoint variables is governed by

$$\dot{\lambda}_x = -\lambda_x\left(\frac{d}{dX}(X\mu(X) - \frac{F}{V}\right) \qquad (6a)$$

$$\dot{\lambda}_v = \lambda_x\frac{FX}{V} \qquad (6b)$$

subject to

$$\lambda_x(t_f) = 1.0 \qquad (7a)$$

$$\lambda_v(t_f) = 0.0 \qquad (7b)$$

Since, the Hamiltonian is linear in the control variable F, the control is determined as

$$\left.\begin{array}{lll} F = F_{max}\,, & \text{when} & \dfrac{\partial H}{\partial F} > 0 \\ F = F_{min}\ (=0), & \text{when} & \dfrac{\partial H}{\partial F} < 0 \end{array}\right] \qquad (8)$$

When H_F vanishes over a finite time interval (a, b) we have the case of singular control,

This can occur when

$$H_F = \dot{H}_F = 0 \qquad (9)$$

The control variable F can be determined in this interval using the information from the higher derivatives. Thus setting

$$\ddot{H}_F = 0 \qquad (10)$$

we obtain $F = \mu(S(X))V$. For the feed rates given by this clearly,

$$\dot{X} = 0$$

$$X(t) = X(a)$$

The value of X, where $\dot{H}_F = 0$, is obtained from

$$\frac{d}{dX}\,\mu(X) = 0 \qquad (11)$$

A detailed derivation of the various expressions can be found in Appendix-2. (11) implies that the kinetic dependency of μ on X,S must exhibit an extremum. An example of a system exhibiting this behaviour is when the reaction is governed by Haldane kinetics i.e., when we have substrate inhibition, Here

$$\mu(S) = \frac{\mu_{max}\, S}{(\alpha + \beta S + \gamma S^2)} \qquad (12)$$

We consider the solution to the problem for the situation when there is no upper bound on F i.e. ($F_{max} = \infty$). Here it is permissible to obtain as large a flow-rate as desired. The optimal policy determined now implies we fill the reactor upto V_i such that now X becomes X_i from $X_o (= X_f)$. The reactor is then filled upto V_f using the singular arc profile along which F varies continuously. Along the singular arc the conditions are such that the reaction rate is a maximum. This reaction is then allowed to run in batch-mode if necessary till the end of the cycle (t_f).

Details of this analysis can be found in Weigand (1981).

The optimal policy of operation obtained using the maximum principle consists of three parts:

(i) Here the manipulated variable F is constant at its upper bound

(ii) Here the manipulated variable F is held constant at its lower bound.

(iii) Here the manipulated variable varies continuously. This region is called the singular arc.

It is usually impractical to vary the manipulated variable such as F(t) continuously as a function of time. In this work we discuss different possible ways in which the system can be operated experimentally by dividing the entire period of operation i.e. cycle into different interval or stages. In the i^{th} stage, the time t is such that $t_{i-1} < t < t_i$ and the manipulated variable is assumed to be maintained constant. The reactor volume and the feed-rate policy in the i^{th} interval are devoted V_i, F_i respectively (Fig.1).

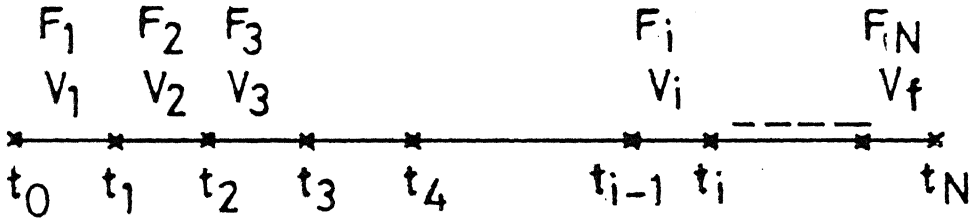


Fig.1. The variables in the different stages of a cycle.

Chapter 4

DIFFERENT APPROXIMATIONS

The optimal profile as determined analytically (Weigand (1981)) consists of three parts (i) rapid fill to an intermediate level (ii) singular control and (iii) batch mode operation. In solving our problem we determine the optimal profile by considering two modes of operation

(a) We allow for the first fill to be a rapid fill and approximate the singular arc. This is called the ASP problem.

(b) We solve for the optimisation problem by approximating the entire cyclic operation in discrete steps. This is called the total optimisation (TO) problem.

4.1 Instantaneous Pulse Feed:

4.1.1 The TO Problem

We now discuss the system behaviour for the TO problem under different approximations.

In this mode of operation we assume that the manipulated variable the feed flow rate can be infinitely large. Consequently, it is possible to add the substrate instantaneously to the reactor at various discrete time instants. This allows us to raise the reactor volume to V_f through a succession of stages. In this mode of operation we have to determine the (i) volume changes at every pulse feed and (ii) the time instants of addition. In Fig. 1 we depict the situation where we have N-pulses to raise the reactor volume from V_o to V_f, at t_o, t_1, ... t_{N-1}.

Clearly, the problem reduces to determining the volumes V_1,

V_2, ... V_{N-1}, the concentrations $X(t_1^+)$, $X(t_2^+)$, ... $X(t_{N-1}^+)$, X_f; such that X_f is maximised. A total of (2N-1) variables have to be determined. The concentration X, evolves in each interval (t_i, t_{i+1}) from $X(t_i^+)$ to $X(t_{i+1}^-)$. The concentrations X at each junction point t_i experiences a discontinuity in this mode of operation. This is determined from the mass balance equations as

$$V_i X(t_{i+1}^-) = V_{i+1} X(t_{i+1}^+) \quad \text{for } i = 1,....N-1 \qquad (13a)$$

Since in each interval or stage the system behaves as a batch reactor, the time interval of each sub-interval can be obtained as

$$\left(t_{i+1} - t_i\right) = \int_{X\left(t_i^+\right)}^{X\left(t_{i+1}^-\right)} \frac{dX}{X\mu(x)} \qquad (13b)$$

So, the total cycle time t_f is given by

$$t_f = \int_{X\left(t_0^+\right)}^{X\left(t_1^-\right)} \frac{dX}{X\mu(X)} + \int_{X\left(t_1^+\right)}^{X\left(t_2^-\right)} \frac{dX}{X\mu(X)} + \ldots + \int_{X\left(t_{n-1}^+\right)}^{X_f} \frac{dX}{X\mu(X)}$$

The variables $X(t_1^-)$ can be eliminated in favour of the variables $X(t_1^+)$ using the relations (13) to yield

$$t_f = \int^{\frac{V_2}{V_1}X\left(t_1^+\right)} \frac{dX}{X\mu(X)} + \int^{\frac{V_3}{V_2}X\left(t_2^+\right)} \frac{dX}{X\mu(X)} + \ldots + \int^{X_f} \frac{dX}{X\mu(X)} \qquad (14)$$

Remembering that t_f is a constant and for a maximum X_f the first derivative with respect to V_i's and $X(t_i^+)$ must equal zero, we obtain on differentiating with respect to $X(t_i^+)$,

$$\mu\left(X(t_i^+)\frac{V_{i+1}}{V_i}\right) = \mu\left(X(t_i^+)\right), \text{ for } i = 1,\ldots N-1 \qquad (15a)$$

Differentiating with respect to V_1 yields

$$\mu\left(X(t_1^+)\frac{V_2}{V_1}\right) = \mu\left(X_f\frac{V_o}{V_1}\right) \qquad (15b)$$

The derivatives with respect to other V_i's yield

$$\mu\left(\frac{V_i}{V_{i-1}}\, X\left(t_{i-1}^+\right)\right) = \mu\left(\frac{V_{i+1}}{V_i}\, X\left(t_i^+\right)\right) \quad \text{for } i=2,\ldots N-1 \qquad (15c)$$

Using these relationships we can establish

$$X\left(t_1^+\right) = X\left(t_2^+\right) = \ldots\ldots X\left(t_{N-1}^+\right) = z \text{ (say)} \qquad (16)$$

Assuming that there can be at most two values of X for which the function $\mu(X)$ attains the same values, we have

$$\frac{V_2}{V_1} = \frac{V_3}{V_2} = \ldots\ldots = \frac{V_N}{V_{N-1}} = r$$

Clearly, it follows

$$X_f\,\frac{V_o}{V_1} = z \qquad (17)$$

(since otherwise the first and last steps will be of non-existent.) Hence we conclude

$$X_f = \frac{zV_f}{r^{N-1}V_o} \tag{18a}$$

This yields

$$t_f = (N-1)\int_z^{rz} \frac{dX}{X\mu(X)} + \int_z^{X_f} \frac{dX}{X\mu(X)} \tag{18b}$$

We solve this equation for z, r, X_f such that

$$\mu(z) = \mu(rz) \tag{18c}$$

4.1.2 The ASP Problem

Weigand found that the optimal control policy was filling the reaction to V_i such that the concentration became X_i (where μ has an extremum) using an infinite flow-rate. The flow-rate was then varied such that X was maintained at X_i. We now assume that the concentration in the reactor after the first pulse is X_i i.e.

$$X(t_o^+) = X_i \tag{19a}$$

The total number of unknowns to be obtained is now (2N-2). These are $X(t_1^+)$, $X(t_2^+)$,....., $X(t_{N-1}^+)$, V_2, ... V_{N-1}, and X_f. The volume V_1 is obtained from the junction condition at t_o^+ as

$$V_1 = \frac{V_o X_f}{X_i} \qquad (19b)$$

Using the conditions for X_f to be a maximum, we have,

$$\mu\left(\frac{V_{i+1}}{V_i} X \left(t_i^+\right)\right) = \mu \left(X\left(t_i^+\right)\right) \text{ for } i = 1, \ldots, N-1 \qquad (20a)$$

$$\mu\left(\frac{V_{i+1}}{V_i} X\left(t_i^+\right)\right) = \mu \left(X\left(t_2^+\right)\right) = \ldots = \mu\left(X \left(t_{N-1}^+\right)\right) \text{ for } i=1,\ldots,N \qquad (20b)$$

From these it follows that

$$\mu(X(t_1^+) = \mu(X(t_2^+)) = \ldots. = \mu(X(t_{N-1}^+)) \qquad (21)$$

Since there are at most two values of X for which $\mu(X)$ attains the same values, we have

$$\frac{V_2}{V_1} = \frac{V_3}{V_2} = \ldots.. = \frac{V_n}{V_{n-1}} = r \text{ (say)}$$

$$t_f = \int_{X_i}^{rz} \frac{dX}{X\mu(X)} + (N-2) \int_{z}^{rz} \frac{dX}{X\mu(X)} + \int_{z}^{X_f} \frac{dX}{X\mu(X)} \qquad (22a)$$

Where

$$\mu(z) = \mu(rz) \qquad (22b)$$

and

$$X_f = \frac{V_f X_i}{V_o r^{N-1}} \qquad (22c)$$

4.2 Finite Feed-Rate (The case of equal sub-intervals)

In the earlier approximation using pulse feeds we tacitly assumed that it is possible to have an infinite rate of substrate addition. The reactor volume can thus change instantaneously from one stage to another and the volume in each stage is a constant. We now consider the situation where in each stage the reactor is operated in a semi-batch mode. Here the substrate is restricted to be added at a constant flow-rate. The feed rates from one sub-interval to another are, however, allowed to be different. Let F_i be the flow-rate in the i^{th} stage. The evolution in the i^{th} stage is governed by

$$\frac{dX}{dt} = X\ \mu(S(X)) - \frac{F_i X}{V_i} \qquad (23a)$$

$$\frac{dV_i}{dt} = F_i \qquad (23b)$$

One objective is to determine the duration of each stage $(t_i - t_{i-1})$ and the flow rate F_i in each stage such that we maximise $X(t_N)$ which is X_f for a fixed draw down ratio (V_f/V_o). In this mode of operation the volume of the reactor is a continuous function of time. Its time derivatives i.e rates of change is discontinuous at the junctions of the different stages.

The concentrations X are continuous functions of time in a cycle. These imply the following conditions for all i

$$X(t_i^-) = X(t_i^+)$$
$$V(t_i^-) = V(t_i^+) \qquad \text{for all i} \qquad (24)$$

In this mode of operation the entire operation is divided into N equal stages. The duration of each stage is fixed and only the N flow-rates have to be determined.

4.2.1 The ASP Problem

In this mode we increase the reactor volume from V_o to V_i ($=V_1$) such that the concentration X_f now becomes X_i The amount of substrate to be added can be obtained from the mass balance,

$$V_1 = V_i = \frac{V_0 X_f}{X_i} \qquad (25)$$

This problem is the same as saying that the initial concentration is fixed at X_i. Here however the initial volume V_i is unknown as the optimum X_f is unknown.

At the end of the N intervals the reactor volume has become V_f. The flow rates F_i in each of the sub-intervals must satisfy the non-linear constraint

$$V_f - \frac{V_o X_f}{X_i} = \sum_{i=1}^{N} F_i \Delta t_i \qquad (26)$$

Since V_f, V_0 are constant and the time of operation is a constant the objective function reduces to (4c).

In each stage the system evolution is governed by (23).

4.2.2 The TO problem.

In this approximation we do not assume any instantaneous addition of substrate at t_o to bring the cell concentration to X_i.

So here the initial cell concentration is the same as the final cell concentration. The different flow-rates F_i's are to be determined such that we maximise $X(t_N)$.

Here since V_f, V_0 are fixed we have the linear constraint

$$V_f - V_0 = \sum_{i=1}^{N} F_i \Delta t_i \qquad (27)$$

The optimisation problem (ASP, TO problems) issolved using sequential quadratic programming. This method is based on linearising the non-linear constraints and constructing a convex quadratic function from the gradients of the objective function. The estimation of the derivatives plays a vital role in the implementation of the algorithm. Rosen and Luus (1991) have discussed different methods of estimating these derivatives. We have obtained these derivatives using two different approaches

In the first method a simple finite difference scheme is used to obtain the derivatives. Thus

$$\frac{\partial X_f}{\partial F_i} = \frac{X_f\left(F_i + \Delta F_i\right) - X_f\left(F_i\right)}{\Delta F_i} \qquad (28)$$

This method involves determining $X(t_N)$ for two different F_i's i.e. $F_i + \Delta F_i$, F_i keeping all other F_j's ($j \neq i$) fixed. The derivative obtained using this approach is very sensitive to the deviation chosen i.e, ΔF_i. This method is hence usually not preferred.

In the second approach we differentiate the model equations analytically and directly obtain $\frac{\partial X_f}{\partial F_i}$. Thus the sensitivity equations are

$$\frac{d}{dt}\left(\frac{\partial X}{\partial F_i}\right) = \frac{\partial}{\partial X}\left(X\mu(s(X) - \frac{F_i X}{V}\right) - \frac{X}{V} + \frac{F_i X}{V^2}\frac{\partial V}{\partial F_i} \qquad (29a)$$

$$\frac{d}{dt}\left(\frac{\partial V}{\partial F_i}\right) = 1 \qquad (29b)$$

These are subject to the initial conditions,

$$\left(\frac{\partial X}{\partial F_i}\right)(t_{i-1}^{+}) = 0 \qquad (30a)$$

$$\frac{\partial V}{\partial F_i}(t_{i-1}^{+}) = 0 \qquad (30b)$$

Integrating (29) along with (23) yield $\frac{\partial X}{\partial F_i}$ at $t=t_i^{-}$

The volume V occurring in the above equations is the volume of the reactor prevailing at the time instant. Thus in the ith time interval it is V_i.

To obtain $\frac{\partial X(t_N)}{\partial F_i}$, we integrate

$$\frac{d}{dt}\left(\frac{\partial X}{\partial F_i}\right) = \frac{\partial}{\partial X}\left(X\mu\,(X) - \frac{F_j X}{V}\right)\frac{\partial X}{\partial F_i} + \frac{F_j X}{V^2}\frac{\partial V}{\partial F_i} \qquad (31a)$$

$$\frac{d}{dt}\left(\frac{\partial V}{\partial F_i}\right) = 0 \qquad (31b)$$

These equations are valid for $t_{j-1} < t < t_j$ for $j > i$

The initial conditions for this set of equations are the same as those at the end conditions of the previous stage. This procedure is used to obtain $\frac{\partial X(t_N)}{\partial F_i}$. More detail of this technique can be found in Levis & Kramer (1985).

The derivatives thus obtained are used in SQP to generate the

next iterate of F_i's. A shooting method technique is used to ensure $X_o = X_f$, for these F_i's. This is necessary since we are considering the repeated fed-batch mode of operation. The numerical algorithm is depicted clearly as a flow sheet in Fig.2.

4.3 Finite feed rate (case of unequal sub-intervals)

So far we have restricted the lengths of each stage to be equal. The duration of each stage was hence predetermined. We now relax this restriction. Now when we discretise the entire operation into N stages we have to determine the N flow-rates F_1, $F_2, \ldots\ldots F_N$ and the N stage durations (t_1-t_0), $(t_2-t_1)\ldots\ldots(t_N-t_{N-1})$. We now have a total of 2 N variables to be determined. In this scenario we again determine the solution to both problems ASP, TO.

4.3.1 The ASP Problem

In this case as explained before we ensure that the initial cell concentration is X_i, by adding an instantaneous charge at $t=t_0$. The initial volume V_1 is obtained from (25).

The entire duration of the batch and the reactor volume are fixed. Thisgives rise to two constraints. The non-linear constraint

$$V_f - \frac{V_0 X_f}{X_i} = \sum_{i=1}^{N} F_i \Delta t_i \qquad (32a)$$

and the linear constraint

$$t_f - t_0 = \sum_{i=1}^{N} \Delta t_i \qquad (32b)$$

The evolution of the variables in each stage is given by (23).

4.3.2 The TO problem

Here the initial volume of the reactor is V_0 and the concentration is $X_o = X_f$. The two constraints now are the nonlinear constraint

$$V_f - V_0 = \sum_{i=1}^{N} F_i \Delta t_i \qquad (33a)$$

and the linear constraint

$$t_f - t_0 = \sum_{i=1}^{N} \Delta t_i \qquad (33b)$$

The optimisation method based on SQP requires the calculation of the derivatives of the objective function with respect to the control variables. The sensitivity method to evaluate the derivatives with respect to the flow-rates has been discussed. We now elaborate on estimating the derivative with respect to stage durations.

We differentiate (23) with respect to time to obtain,

$$\frac{d}{dt}\left(\frac{\partial X}{\partial \Delta t_i}\right) = \frac{\partial}{\partial X}\left(X\mu\,(X) - \frac{F_{i+1}\,X}{V}\right)\frac{\partial X}{\partial \Delta t_i} - \frac{F_{i+1}\,X}{V^2}\,\frac{\partial V}{\partial \Delta t_i} \qquad (34a)$$

$$\frac{d}{dt}\left(\frac{\partial V}{\partial \Delta t_i}\right) = 0 \qquad (34b)$$

These equations govern the evolution of $\frac{\partial X}{\partial \Delta t_i}$ in $t_i < t < t_{i+1}$.

They are integrated subject to the initial condition

$$\left.\frac{\partial X}{\partial (\Delta t_i)}\right|_{t=t_i^+} = \left.\left(X\mu\ (X) - \frac{F_i\ X}{V}\right)\right|_{t=t_i^-} \qquad (35a)$$

$$\left.\frac{\partial V}{\partial (\Delta t_i)}\right|_{t=t_i^+} = F_i \qquad (35b)$$

The integration of these equations upto the N^{th} stage gives us the required derivative $\frac{dX\ (t_N)}{d(\Delta t_i)}$, where Δt_i is the stage duration of the i^{th} stage.

4.4 Transforming a Non-Linear Constraint to a Linear Constraint:

For a fixed final volume of reactor and a fixed time of operation, the stage durations and the flow-rates during the stages are constrained by (32a) and (33a).

For the case where the sub-intervals i.e. stage durations have to be determined this is a non-linear constraint,

This is true when the variables to be obtained are the F_i's, Δt_i's.

An alternative method is to look at the total amount added during a stage U_i as the process variable. Since the flow-rate in each stage F_i is a constant, we have

$$U_i = F_i \Delta t_i \qquad (36a)$$

The non-linear constraint now is modified to the linear constraint

$$\sum_{i=1}^{N} U_i = V_f - V_o \qquad (36b)$$

The 2N variables to be obtained now are the N U_i's and the N Δt_i's. The method of SQP is based on linearising non-linear constraints. Since the constraint in terms of the U_i's is linear to begin with this transformation renders the numerical algorithm more efficient.

The derivatives with respect to the U_i's needs to be obtained. This can be obtained in terms of the derivatives with respect to F_i's, Δt_i's using the chain rule of differentiation.

Let the charge added over the interval Δt_i be denoted by U_i. Since the control variables are U_i's, Δt_i's, the derivative of interest is evaluated for a constant value of all the other parameters.

Treating X_f as a function of F_i's, Δt_i's, we obtain

$$dX_f = \sum_{i=1}^{N} \frac{\partial X_f}{\partial \Delta t_i}\bigg|_{F_i} d\Delta t_i + \sum_{i=1}^{N} \frac{\partial X_f}{\partial F_i}\bigg|_{\Delta t_i} dF_i \qquad (37a)$$

Treating X_f as a function of U_i's, Δt_i's, we obtain

$$dX_f = \sum_{i=1}^{N} \frac{\partial X_f}{\partial \Delta t_i}\bigg|_{U_i} d\Delta t_i + \sum_{i=1}^{N} \frac{\partial X_f}{\partial U_i}\bigg|_{\Delta t_i} dU_i \qquad (37b)$$

Since U_i is dependent upon the F_i's and Δt_i's we again have

$$dU_i = \frac{\partial U_i}{\partial F_i}\bigg|_{\Delta t_i} dF_i + \frac{\partial U_i}{\partial \Delta t_i}\bigg|_{F_i} d\Delta t_i \qquad (38)$$

Substituting this in (37b)and equating the coefficients of $d\Delta t_i$'s and dF_i's we obtain

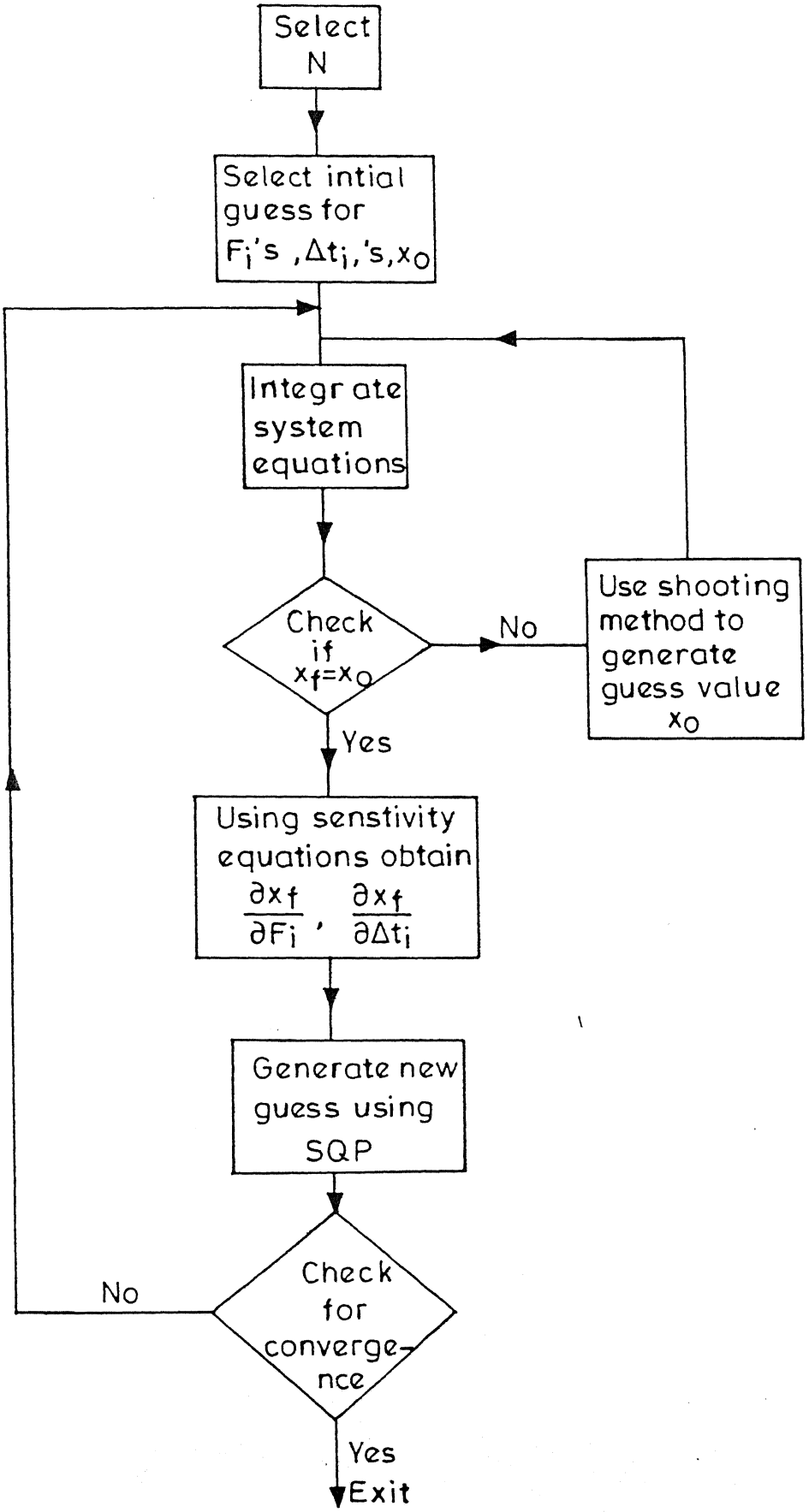
$$\left.\frac{\partial X_f}{\partial U_i}\right|_{u_{i\neq j},\Delta t_i} = \left.\left(\frac{\partial X_f}{\partial F_i}\right)\right|_{F_{i\neq j},\Delta t_i} \frac{1}{\Delta t_i} \qquad (39a)$$

$$\left.\frac{\partial X_f}{\partial \Delta t_i}\right|_{U_i\ \Delta t_{i\neq j}} = \left.\frac{\partial X_f}{\partial \Delta t_i}\right|_{F_i,\Delta t_{i\neq j}} - \left.\frac{\partial X_f}{\partial U_i}\right|_{U_{j\neq i},\Delta t_i} \qquad (39b)$$

(when U_i's, Δt_i's are control variables)

The derivatives required are computed using the derivatives evaluated with F_i's and Δt_i's as process variables from (29) and (34).

The simulation of the system with these linear constraints is such that the upper bound specified now is on U_i's, as opposed to F's in the earlier approach. It is also important while using the linear constraints formulation to impose a non-zero minimum bound on the Δt_i's. This is necessary as we want to avoid a time interval from going to zero. It is hence not possible to obtain a direct comparison and validation of the results using the two approaches.


Select N
Select intial guess for F_i's , Δt_i,'s, x_o
Integr ate system equations
Check if $x_f = x_o$
No
Use shooting method to generate guess value x_o
Yes
Using senstivity equations obtain $\frac{\partial x_f}{\partial F_i}$, $\frac{\partial x_f}{\partial \Delta t_i}$
Generate new guess using SQP
Check for converge-nce
No
Yes
Exit

Chapter 5

MAXIMISING PROTEIN FORMATION IN A NON-REPEATED FED-BATCH

So far we have discussed the optimum feeding strategy which results in maximization of biomass formed in a biochemical reactor. The time of operation, the initial and final reactor volumes were fixed. The reactor was operated in a repeated fed-batch mode.

A second class of problems concerns us with the optimisation of the product formed in a biochemical reactor. Park and Ramirez (1988) considered the problem of maximizing a heterologous protein secreted in a fed-batch reactor, using a model host yeast SEY2102. The model secretory protein is SUC2-S2.

The system evolution is governed by the set of five ordinary differential equations

$$\dot{P}_M = A(S)(P_T - P_M) - \frac{F}{M} P_M \qquad (40a)$$

$$\dot{P}_T = B(S)X - \frac{F}{V} P_T \qquad (40b)$$

$$\dot{X} = C(S)X - \frac{F}{V}X \qquad (40c)$$

$$\dot{S} = - YC(S)X + \frac{F}{V}(S_F - S) \qquad (40d)$$

$$\dot{V} = F \qquad (40e)$$

with $A(S) = \dfrac{4.75C(S)}{.12+C(S)}$

$$B(S) = \frac{Se^{-5.05}}{0.1 + S}$$

$$C(S) = \frac{21.87}{(S+0.4)(S+62.5)}$$

In these equations P_M (P_T) represents the level of secreted (total) protein in the reactor.

The objective function is to maximize the total secreted protein SUC2-S2, i.e.

$$J = P_M(t_f)V(t_f) \qquad (41)$$

Park and Ramirez (1988) solved this problem using the maximum principle. They considered the operation of a single cycle of the batch operation i.e. operation in the non-repeated fed-batch mode. They obtained the existence of multiple singular arcs as their optimal feeding strategy. They investigated the reactor performance for two different cycle times of 7.5 hrs and 15 hrs.

The final volume of the reactor in this mode is not fixed and this results in the objective function being defined as in (41). This study was based on system performance on a single cycle of operation. Consequently the initial conditions of the reactor affect the performance.

We extend and apply the numerical methods of the earlier section to analyse this problem. The algorithm discussed in theearlier (Fig.2)section is modified. The 'shooting method' step is deleted, since now the terminal conditions i.e. concentrations at the end of the cycle do not necessarily have to be equal to the initial conditions. We have solved this problem only for the case of 'N' equal sub-intervals. Here consequently the control variables to be determined are the 'N' F_i's. Since the final volume is not fixed, the non-linear constraint (33a) is not valid

anymore.

The derivative of the objective function with respect to the flow-rates F's were calculated using the sensitivity equations as discussed earlier.

An important feature of this problem is at the theoretical analytical profile consists of two singular arcs. More specifically the system starts with a singular control, is followed by an interval where the reaction is in batch mode and is then again followed by a singular arc.

Chapter 6

RESULTS AND DISCUSSION

We now discuss the results obtained using the different approximations presented in the earlier section for the two problems.

The optimisation problem as posed in (3) and (4)can be solved using the maximum principles. Weigand (1981) obtained the relationship

$$t_f = \frac{1}{\mu(X)} \ln\left(\frac{V_f X_i}{V_o X_f}\right) + \int_{X_i}^{X_f} \frac{dX}{X\,\mu(X)} \qquad (41)$$

This relationship is derived in Appendix 2.This relates the time of operation t_f to X_f for a fixed V_f, V_o at the optimum conditions. Weigand (1981) obtained this relationship for a fixed X_f and minimising the time t_f. This relationship is also true for maximising X_f for a fixed t_f. The variation of the control parameter F(t) versus time and the corresponding change in volume are depicted in Figures 3 a,b,. The biomass concentration X_f = 1.95. This is the same as the initial concentration X_o. At time t_o a pulse is added instantaneously bringing the volume upto V_i and maintainng the concentration X at X_i, where the rate is a maximum. The system proceeds along the singular arc for 7.922 hr and the final batch operation proceeds upto 10.2965 hrs.The parameters chosen for the simulation are α = 25, β = 62.9, γ = 1.0, μ_{max}= 21.87, S_F = 10, Y = 1/5, V_o =1.0 , V_f =21.0, t_f =10.2965. The optimal solution X_f = 1.95.

The optimal control policy is hence such that X_i is maintained at X_i where the reaction rate is a maximum. The singular arc is terminated once the volume of the reactor attains the final value V_f. The reactor volume increases in the singular arc region till it attains V_f. The reactor volume is then invariant till the end of the batch operation.

In Fig. 4a we present results of the approximation of singular arc using discrete pulses. Here we assume that a first pulse is added at t_o such that it brings the concentration to X_i. The results for N = 6 pulses, and N=16 pulses are depicted in Figures 4 a,b. Here we have plotted the volume of the reactor after the addition of each pulse. The volume changes discontinuously at the points where the pulses were added. These are the best possible approximation of Fig. 3b for agiven N.

The duration of the stages here when the reactor volume is V_2, $V_3 \ldots$, V_{n-1} are all equal. The first and last stages are of unequal duration as can be seen in Fig. 4a. The duration of the last batch stage compares favourably with the prediction in Fig. 3a.

The ratio of the volumes V_{i+1}/V_i is constant for N = 16. The addition of the pulses is such that the biomass concentration after each pulse attains a constant value, X_c. This value X_c tends to X_i as we increase N. The profile shown in Figures 4, approach the analytical profile of Fig.3b as we increase N. The objective function was computed as X_f = 1.9072, and 1.9142 when N = 6, 16 respectively. In Figure 5a,b we have depicted the results for the total optimisation problem for the two cases of N = 6, 16.

Here the addition of the first pulse at t_o is not constrained to convert the biomass from X_f to X_i. Here the duration of the first N-1, stages are equal. The volume ratios V_i/V_{i-1} are again constant for N = 16. The final batch operation duration matches the results depicted in Fig. 3b. Once again the biomass concentrations after the addition of each pulse is a constant. This constant tends to X_i as $N \longrightarrow \infty$. The biomass concentration at t_f for N=6, 16 ar X_f = 1.909, 1.915 respectively. These are both marginally better than the results of the ASP problem depicted in Fig. 4a,b. This is to be expected since in the TO problem we do not constrain the first pulse to be such that it converts X_f to X_i. Hence the ASP problem can be viewed as the TO problem with a constraint. The objective function for the ASP is hence lesser than that of TO for a given N. In Appendix 3 we show how the relationship (41) can be obtained as a limiting case of (18a).

We now discuss the results when the entire batch operation is divided into N stages. The stages are of equal duration and the flow-rates in each stage is a constant. The flow rate F is constrained to be less than F_{max}(10.0). For a fair comparison we have simulated the ASP problem, for N = 4, stages and TO problem for N=5 stages. Here there is an instantaneous pulse at t_o, such that $X(t_o^+)= X_i$. The flow-rates (Fig.6) for the ASP problem increase as we go through successive stages. N=1,2,3. The last stage is operated in batch mode with F= 0. The increasing flow-rate captures the trend of the singular arc depicted in Fig.3a. The constraint on the flow-rate $F < F_{max}$, can be incorported elegantly using this approach. The results for the TO

problem are depicted in Fig. 7. Here we have used N = 5, to take into account the instantaneous charge at t = 0 (t_o) of the ASP problem. Here the first stage runs with an F of (1.9). There is than a drop in the value of F at the second stage. The flow-rate behaviour captures the features of the singular arc predicted theoretically. The flow-rate in the first stage here is not necessarily equal to F_{max}. This is only to be expected since we have fixed the duration of the first stage.

The objective function X_f for the TO problem (1.8882) is lower than the X_f for the ASP problem (1.9148). This is because in the ASP problem, we have no constraint on F for the first stage which is an instantaneous addition.

The results of the simulations for the case of unequal time intervals are depicted in Fig. 8,9. The ASP problem has been solved for N=4. The flow-rates F_i's in each stage shows an increasing trend capturing the feature of the singular arc. The results of the TO problem are depicted in Fig. 9 for N=5. Here the duration of the first stage is not fixed externally. From the results the optimum profile is such that we have close to an instantaneous charge for the first-stage. Here the stage duration is low and the flow-rate is the maximum permissible. The flow-rate in the second stage drops to a low-value and increases in the next two stages. The last stage again is a batch mode. The instantaneous filling at t=0 (subject to the constraint on F), has been captured by our method. Once again the objective function of the ASP problem (1.9162) is better than that of the TO problem (1.91407).

In Fig.10a, we have shown the results of the total optimisation problem, when using the linear constraints. Here the amount of charge added in a stage is considered the control parameter. Here again N was chosen as 5. The optimum profile has been represented in terms of F_i's again to facilitate a comparison with Fig.7b. The two profiles are almost identical as can be seen. The advantage with the linear constraints is that the constraints are identically satisfied. This results in a faster convergence. The number of iterations needed to converge to the solution here was 31 as compared to 205 with the non-liner constraints. The F in the first interval is 19.95020 and the corresponding optimum objective function is X_f = 1.913889.

Fig.10b represents the X variation for the optimal flow-rate profile that we depict in Fig. 10a. The optimal feed rate is hence such that we maintain X close to X_i till the reactor is filled.

The numerical approach discussed allows us to discuss the optimal strategy when F_{max} is lower than the maximum value on the singular arc. We ensure that it is high enough to satisfy the constraints. This enables us to study how the optimal solution now does not emulate the singular arc.

Figs.11a and 11b are for the TO problem using nonlinear constraints. In Fig. 11a, F_{max} is 3 and for Fig. 11b F_{max} is 4. Here we have chosen the $F_{max} < \max (F_{sing})$ as predicted in Fig.3a. This allows us to see the effect on singular profile. When F_{max} is 4, F in the 4th stage is 4 while it is 4.3137 for F_{max} = 20. For F_{max} = 3, the last two stages merge with each other. For F_{max}

= 3,4, the optimum X_f is 1.89881 and 1.9046 respectively. It is clear from this that as we increase F_{max}, X_f increases and the algorithm approaches optimal profile.

Figs. 12a, 12b and 12c are the plots of optimal control policy for the case where we have converted the nonlinear constraint to a linear one with the upper bound on u being u_{max} = 7.0, 6.3 and 5.0 respectively. The corresponding objective functions are 1.9052, 1.9027 and 1.8825.

We finally simulate the system for maximising the product formed in a biochemical system. We investigate the problem of maximisation of the protein formed as studied by Park and Ramirez. The optimal control profile as obtained in their study consisted of a singular arc, followed by a batch operation and again followed by a singular arc (Figs.13a and 13b) for two different times of operation 7.5 hours and 15 hours. We now show how the methodology proposed here can be used to approximate optimal control profile.

We have maximised the total amount of protein formed, for a fixed time of operation of 7.5 hrs and 15 hrs. For t_f = 7.5 hrs, we have carried out simulations when the entire duration has been divided into equal intervals with constant F's in each. The results for N = 5, 10 are depicted in Figs.14a,b. We clearly see that there is a singular arc followed by a batch and followed by a second singular arc. The objective function for N=5, 10 respectively are 3.102, 3.1233.

From t_f = 15 hrs, we show the results of our simulations in Figs. 15a, b, for N= 5, 10. For N=5, the flow rate shows an

increasing trend inthe first three intervals. It then decreases and shows an increasing trend again in the next two stages. The in between batch mode is not captured here, since it lies between the third and fourth stages. For N=10, however the in between batch mode is captured in the 7th stage. Here we can clearly see that the two singular arcs are obtained. The objective functions for N=5,10 are 29.006, 29.6315 respectively.

In Figs. 16a,b we show the variation of the objective function ($P_m V$) and ($P_T V$) for the optimal operation for N=10. The variationof these quantities is similar to that observed by Park and Ramirez.

The validity of the numerical scheme for this system has been established. The dimension of this system is larger than the earlier problem (3a,b) where we maximised biomass production. We found our algorithm to be faster for this case than in the earlier problem. This arises because the approach now does not the shooting method to ensure that the initial and final state of the system are equal.

The number of divisions N has a significant effect on the objective function here since the singular control occurs over a significant portion of the cycle time.

The computations using our algorithms were performed with a variety of initial guesses. We found that our system converged to the same optimal profile from each initial guess.

In our work we have assumed that $F_{max} \geq \frac{V_f - V_o}{t_f}$

This ensures us that we can fill up the reactor to V_f in the allotted time t_f.

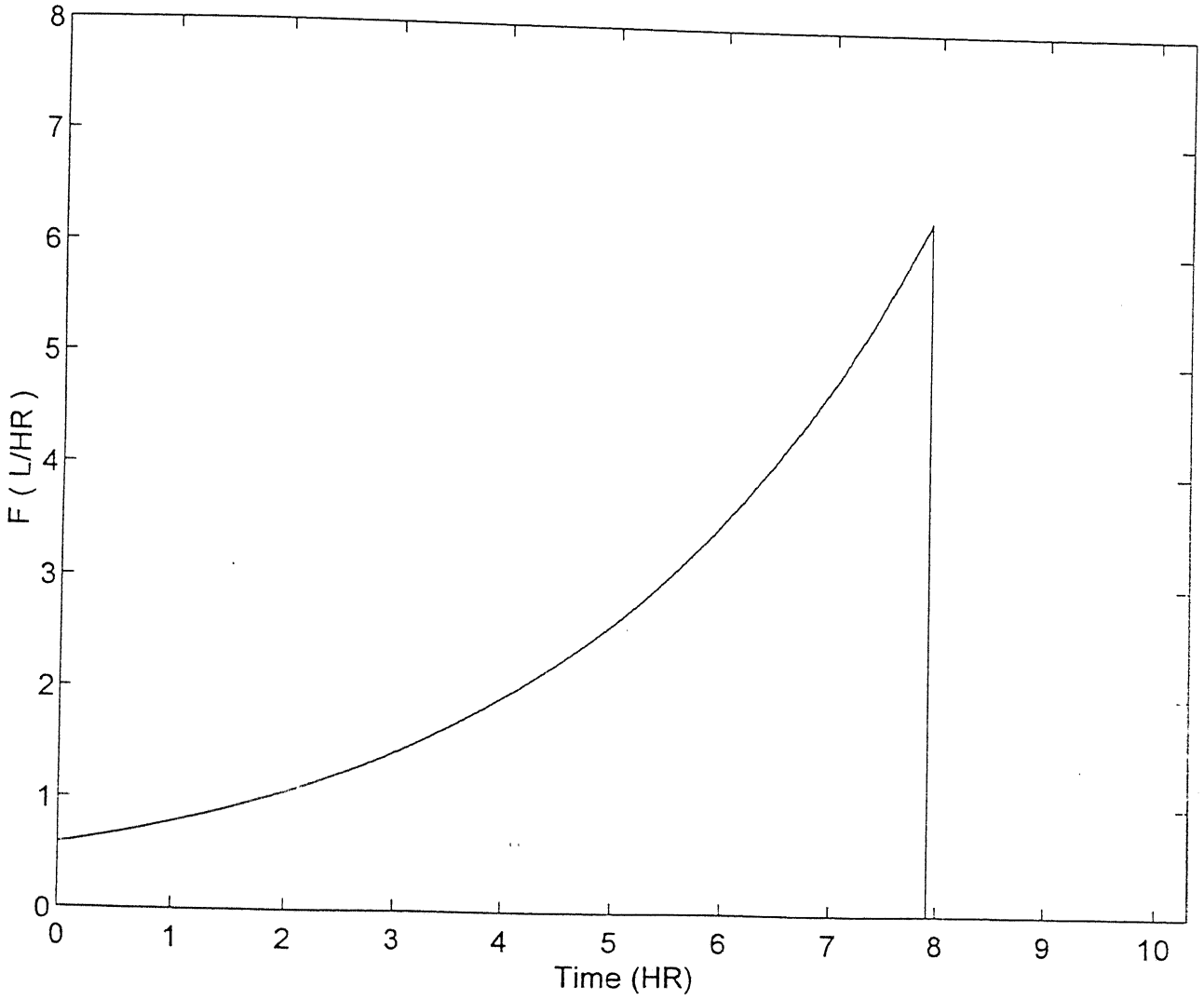


Fig3a. Optimal control policy determined using maximum principle.

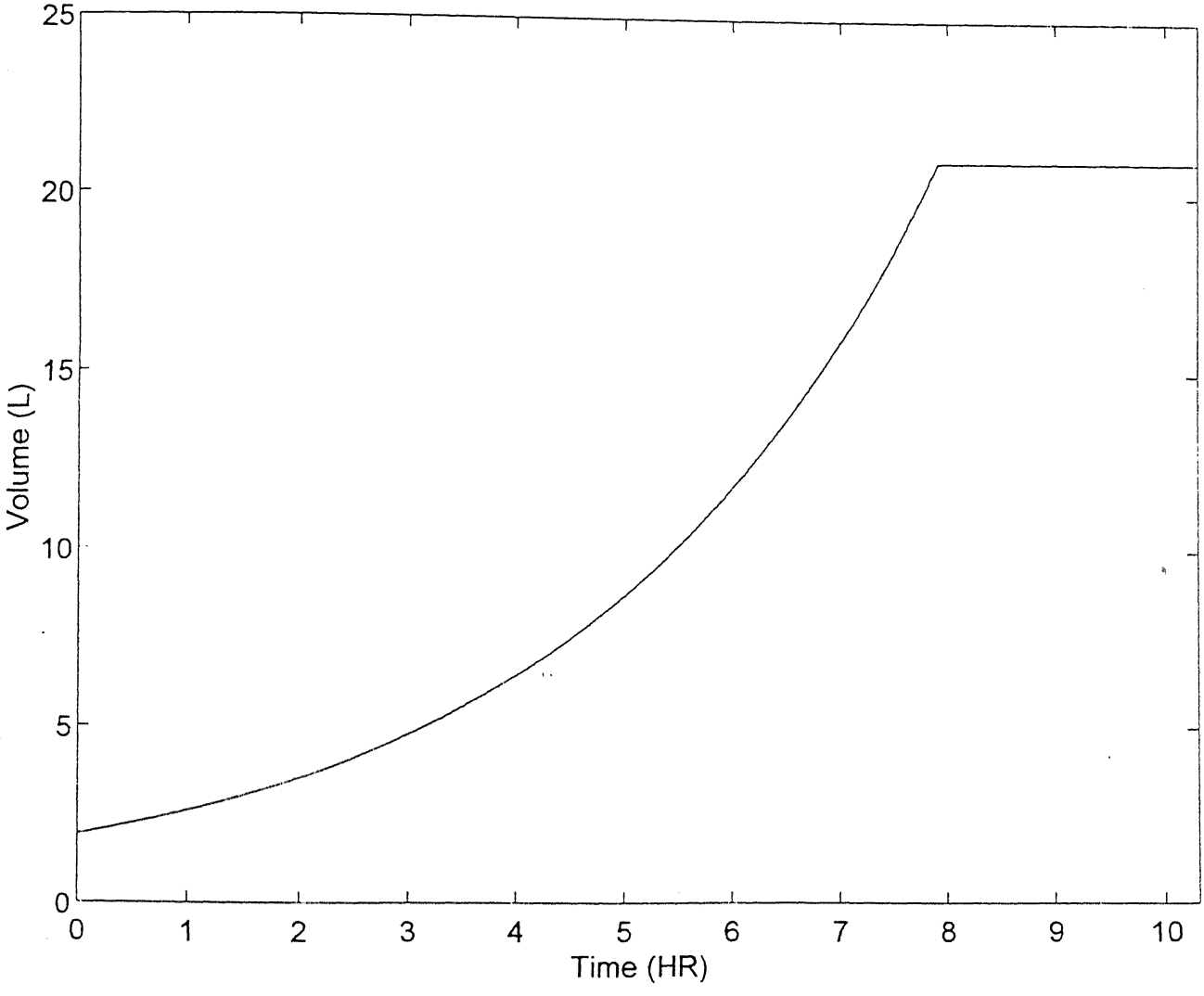


Fig3b. Volume profile for the optimal policy of Fig. 3a

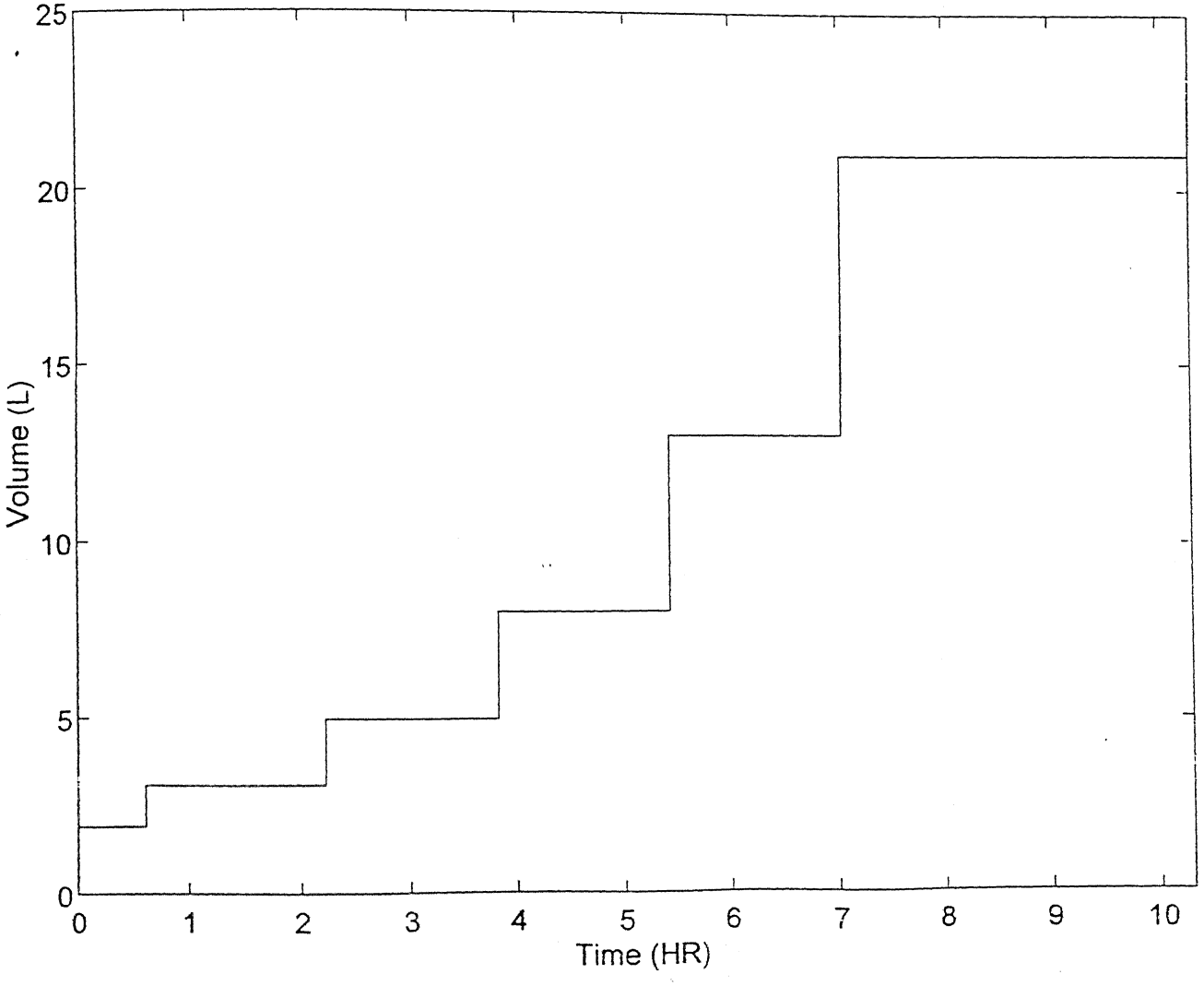


Fig4a. The approximation of the singular arc using discrete pulses for N=6

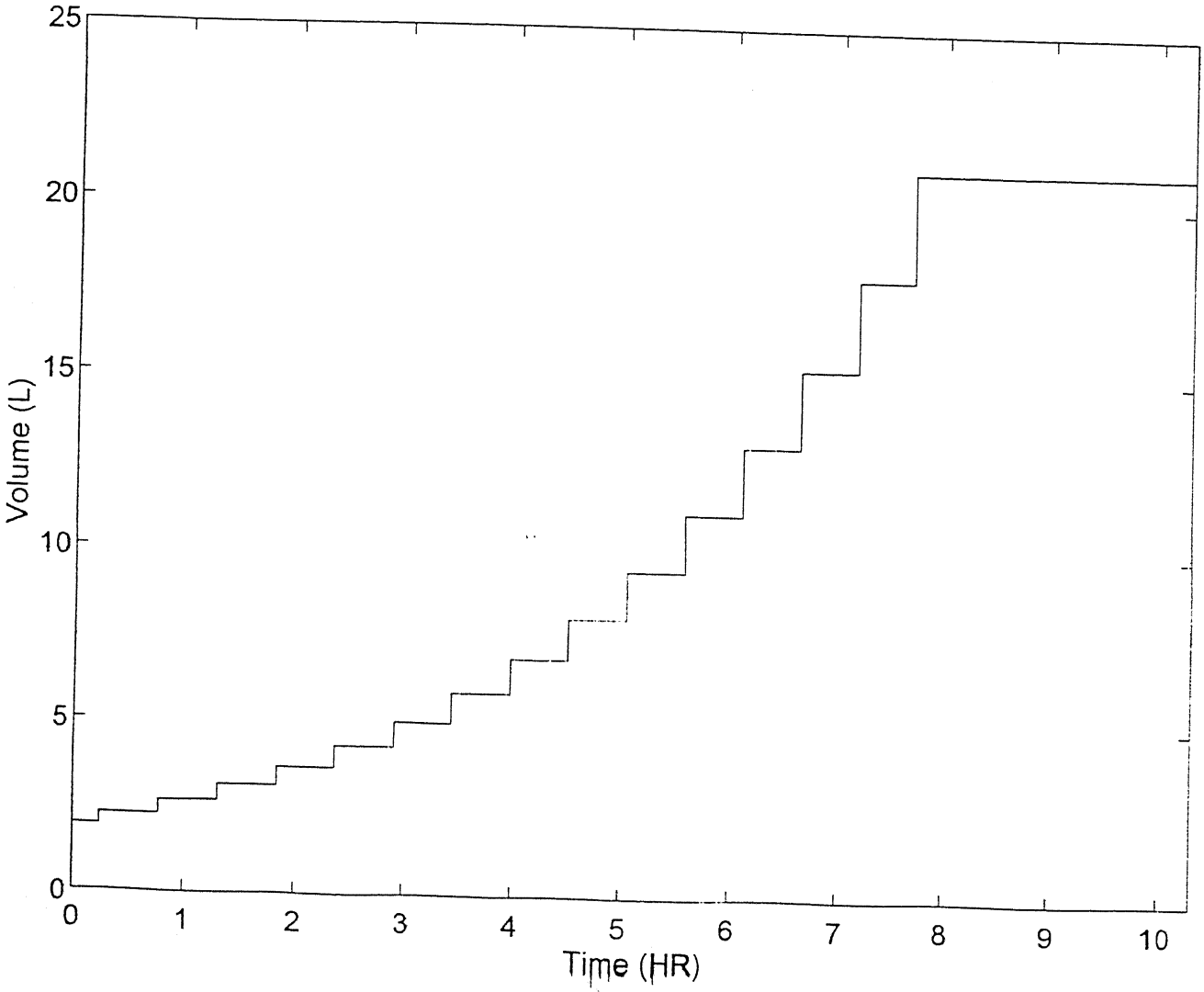


Fig4b. The approximation of the singular arc using discrete pulses for N=16

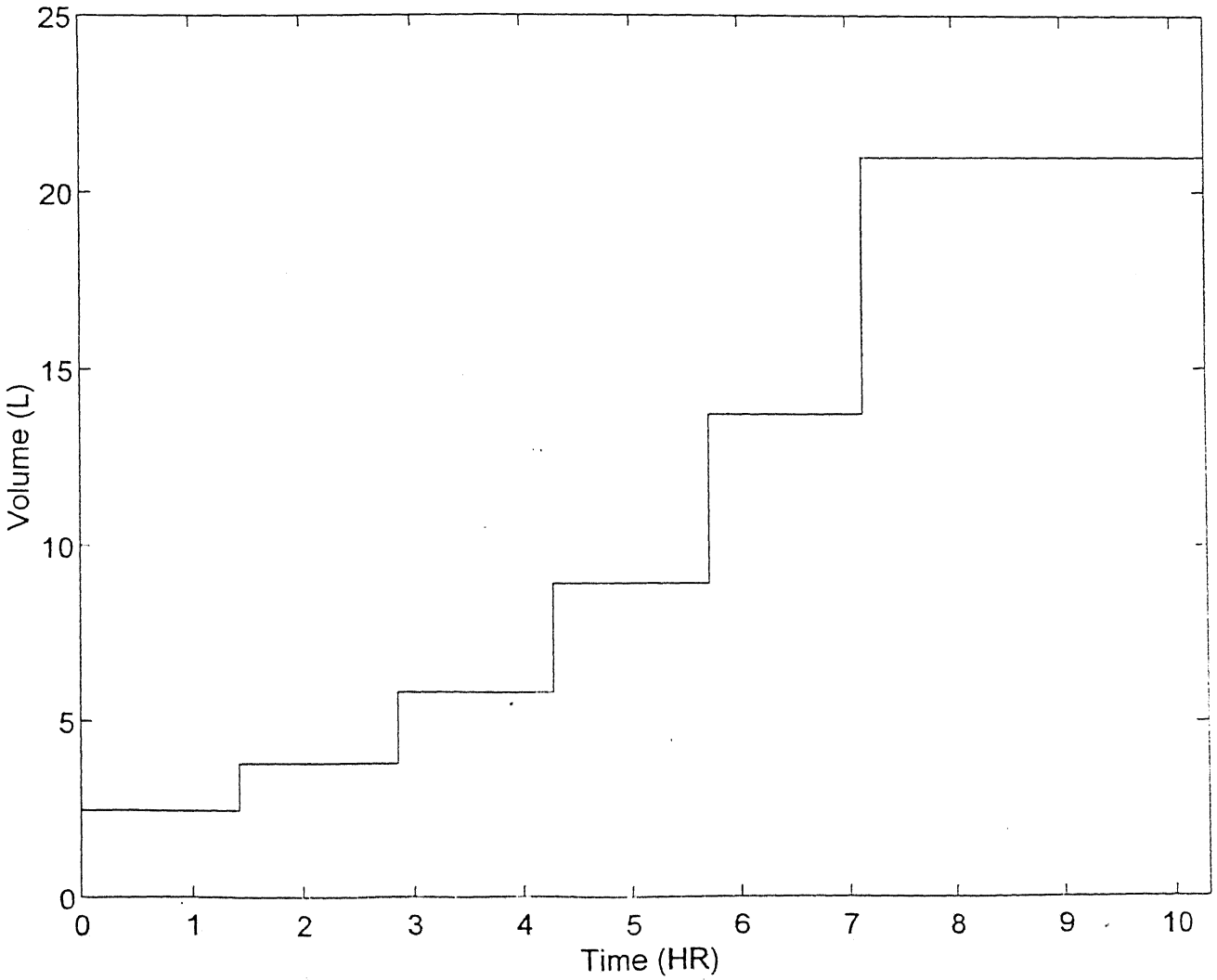


Fig5a. Total Optimisation problem using discrete pulses for N=6

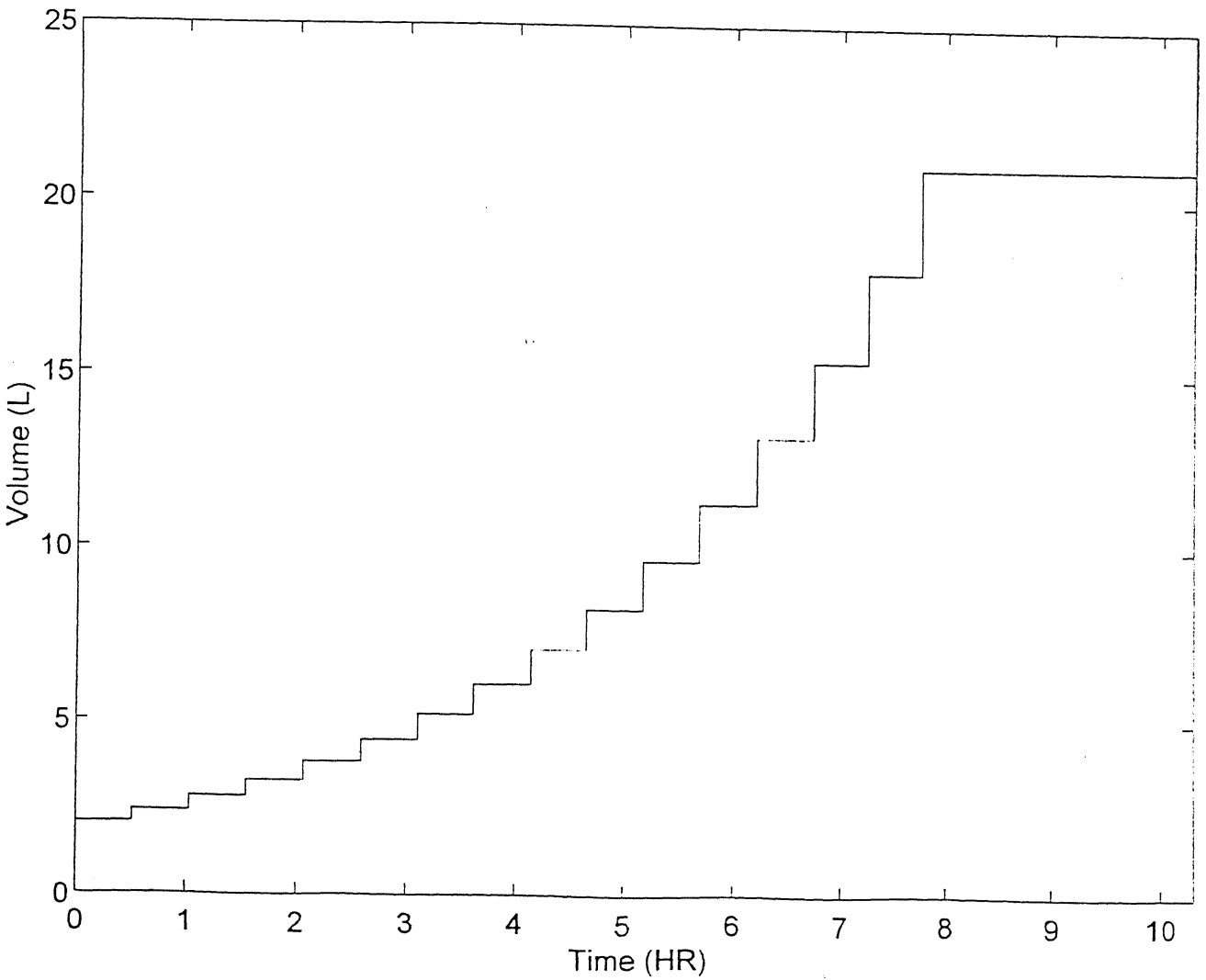


Fig5b. Total Optimisation problem using discrete pulses for N=16

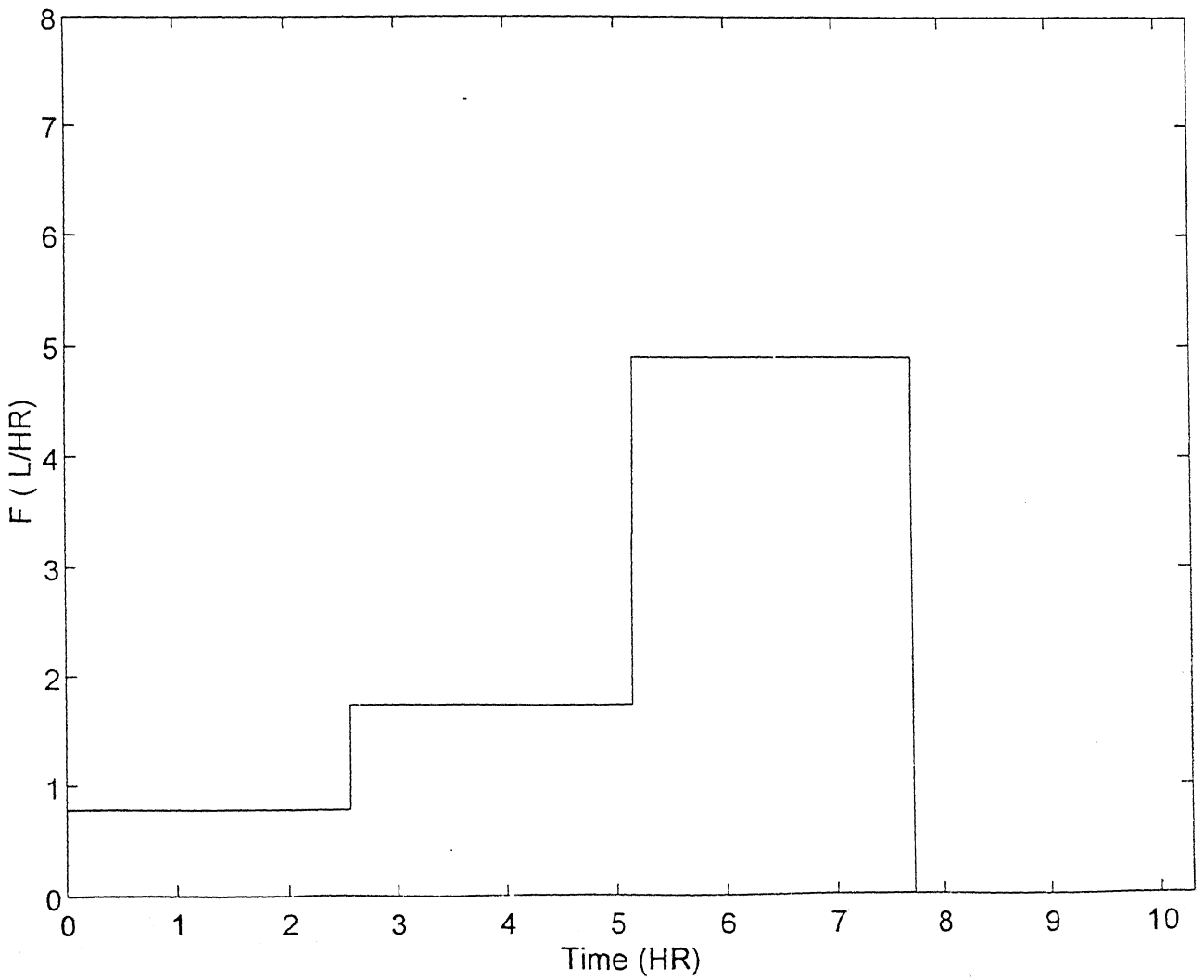


Fig6. The approximation of singular arc using piece-wise constant flow rate in each stage for equal stage duration N=4 , F_{max}=10.0

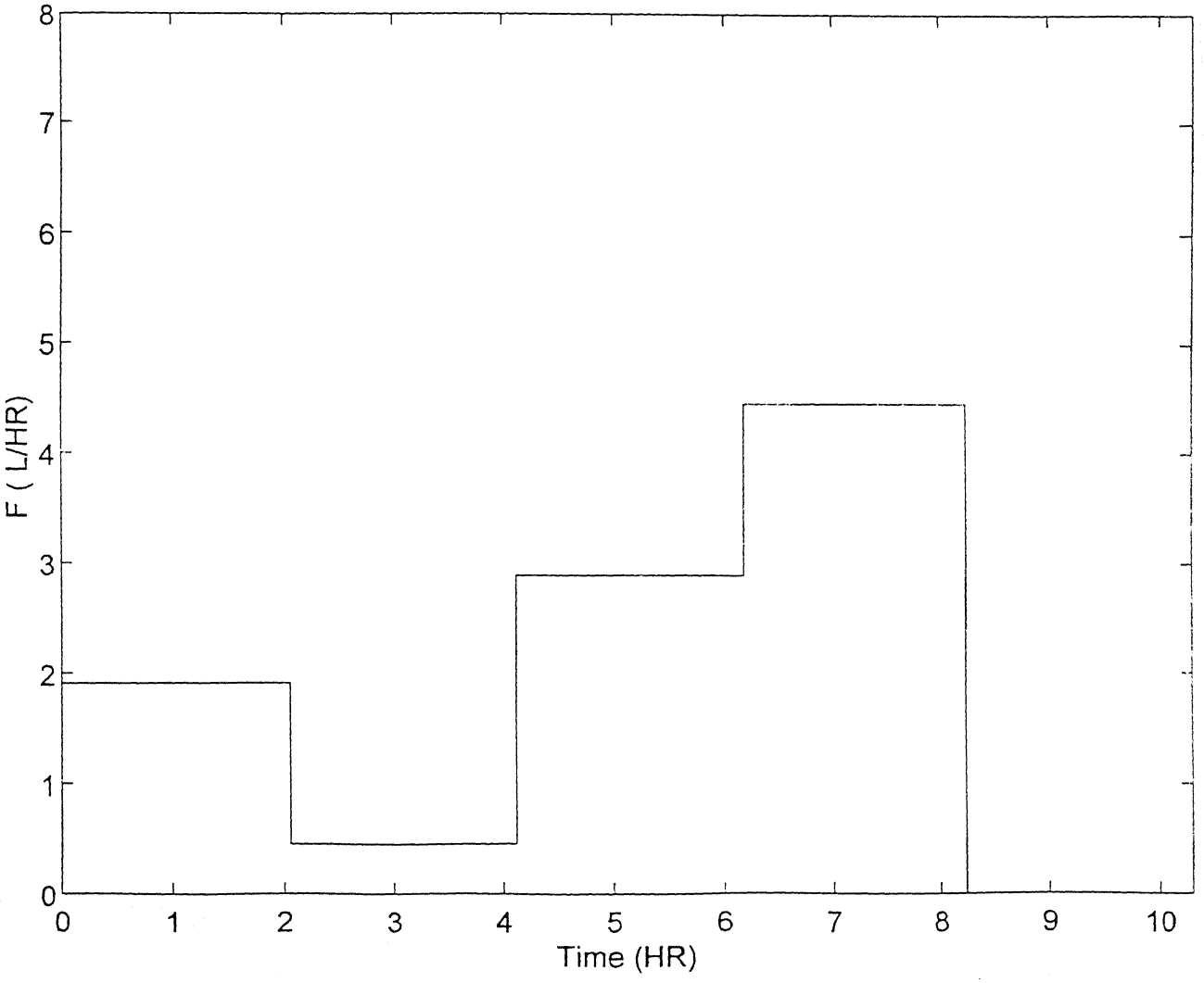


Fig7. The total optimisation problem using piece-wise constant flow rate in each stage for equal stage duration N=5 , F_{max}=10.0

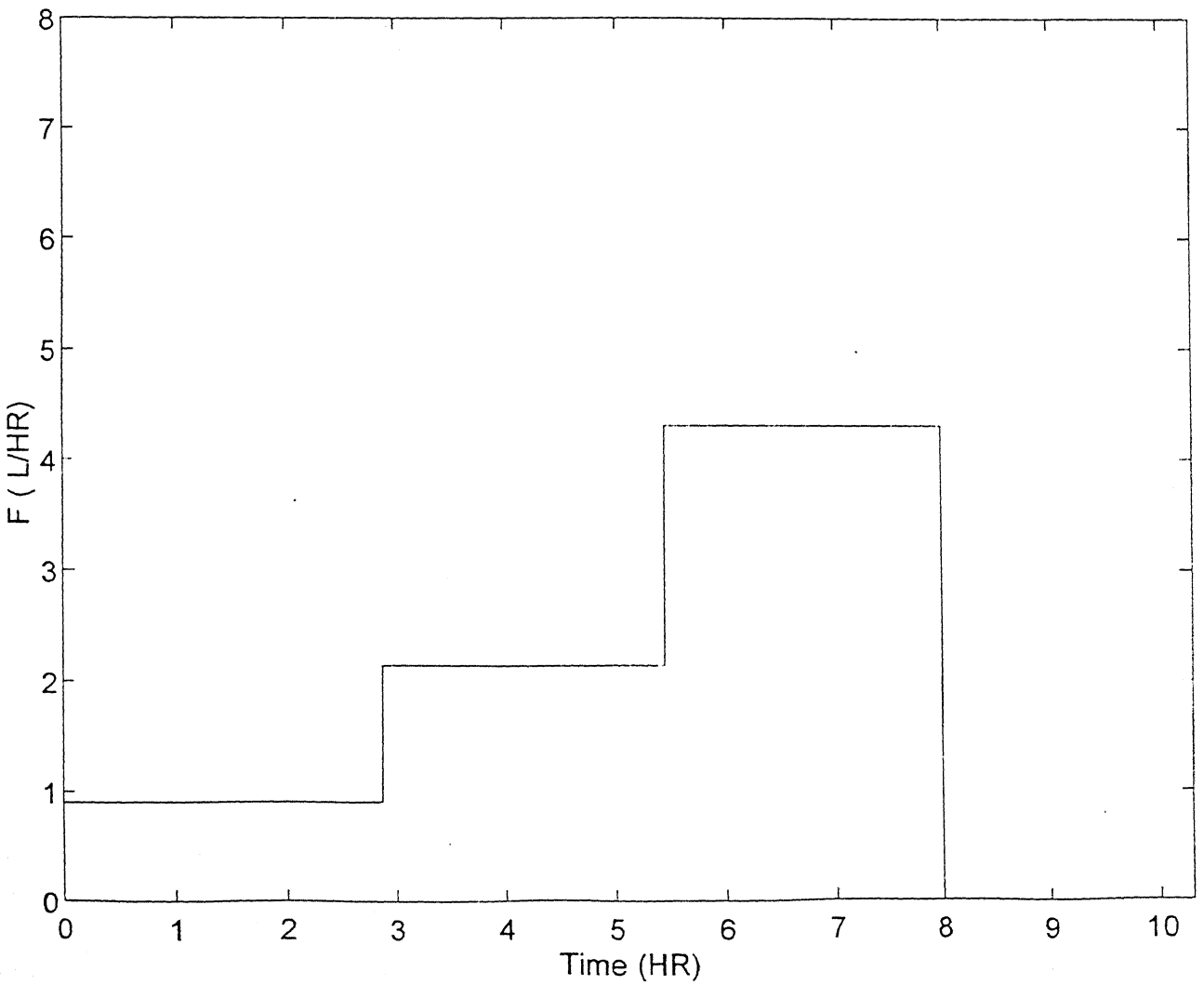


Fig.8. The approximation of singular arc using piece-wise constant flow rate in each stage , unequal stage durations N=4 , F_{max}=10.0.

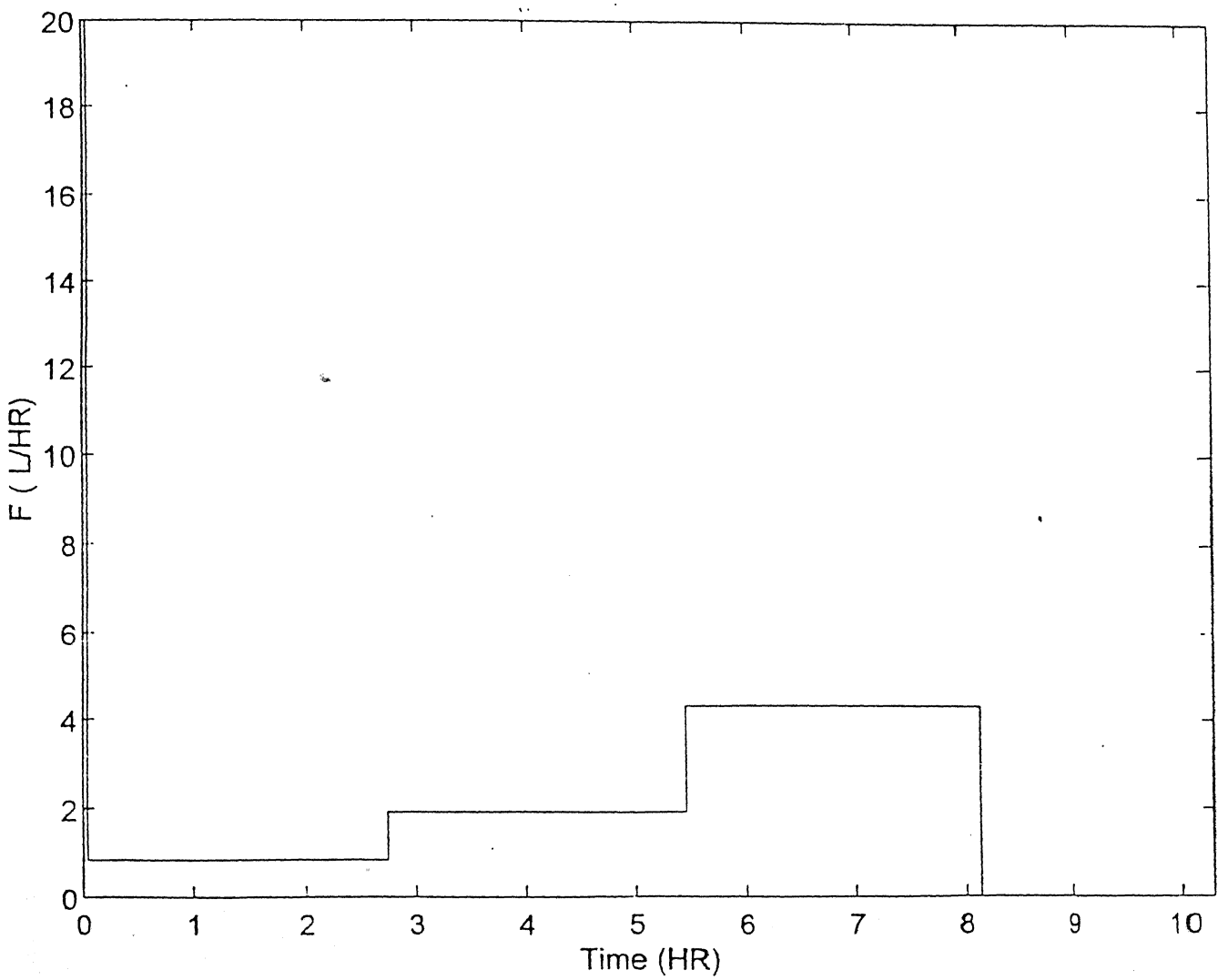


Fig9. The Total optimisation problem using piece-wise constant flow rate in each stage , unequal stage durations N=5 , F_{max}=20.0

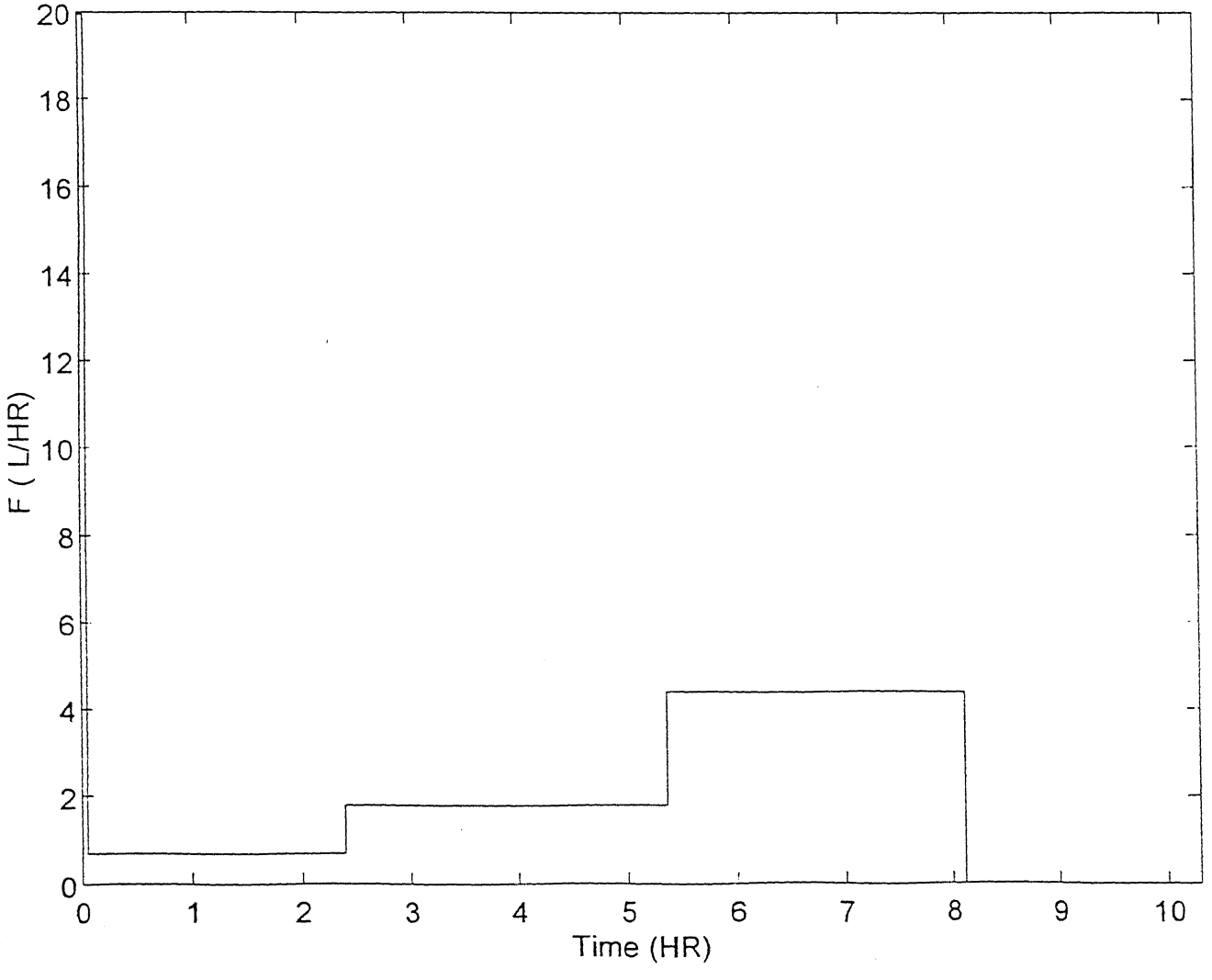


Fig10a. The total optimisation problem using linear constraints (piece-wise constant flow rate in each stage, unequal stage durations) N=5, U_{max}=20.0, Δt_{min} = 0.05, control variable profile

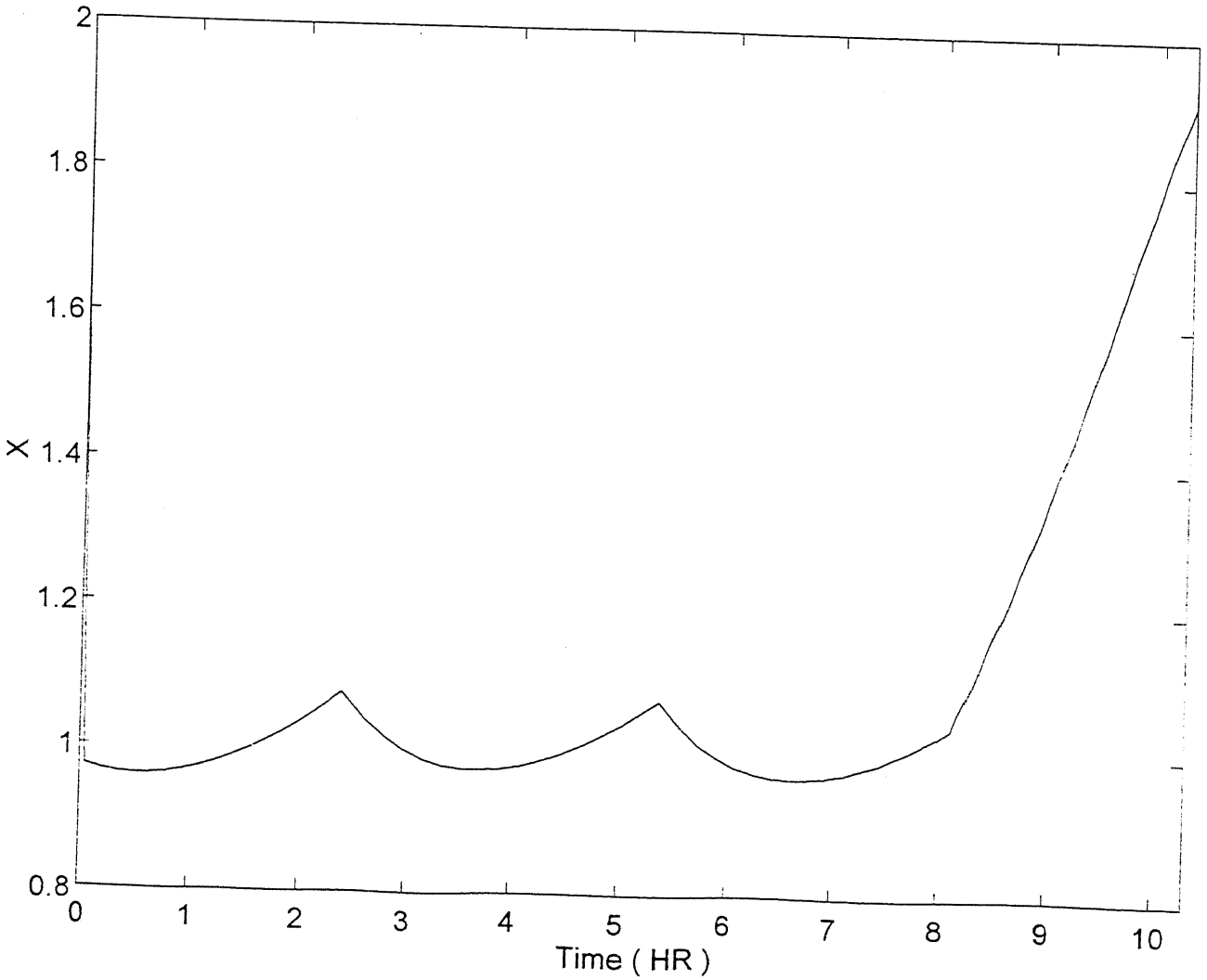
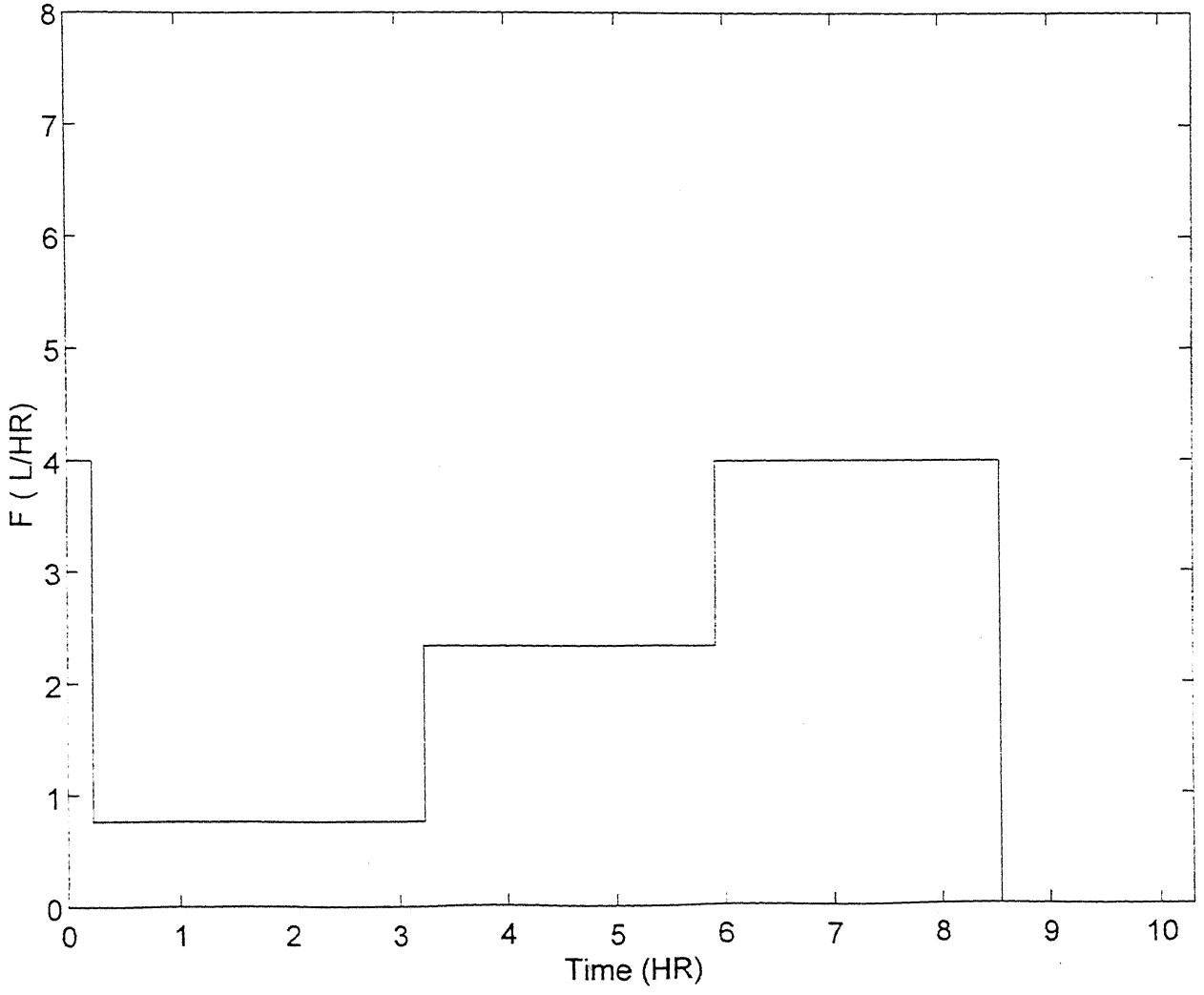


Fig.10b. The Total optimisation problem using linear constraints (piece-wise constant flow rate in each stage , unequal stage durations) N=5 , U_{max}=20.0 , Δt_{min} = 0.05 , variation of X.



Figlla The total optimisation problem using non-linear constraints F_{max}=4.0

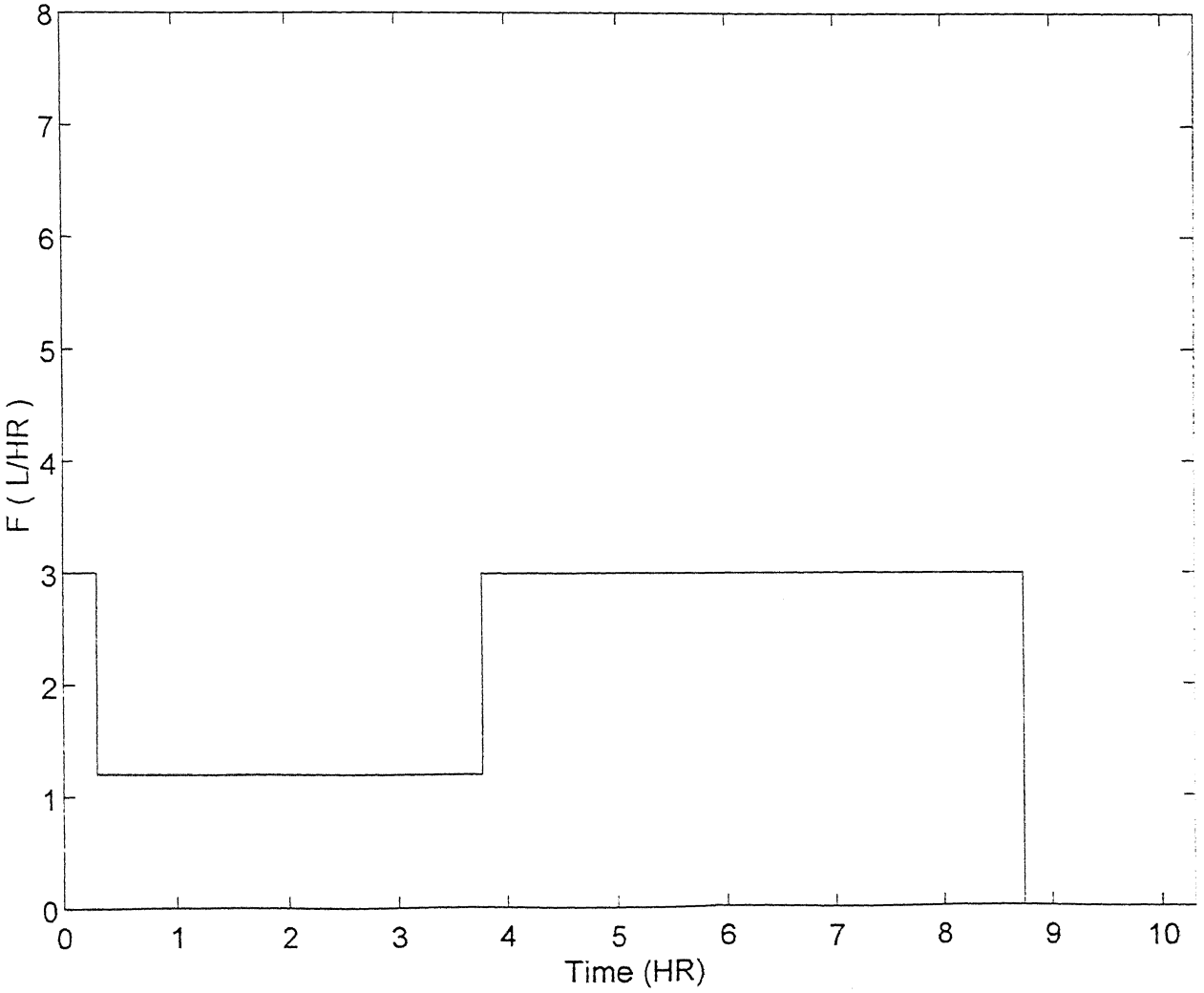


Fig11b The total optimisation problem using non-linear constraints F_{max}=3.0

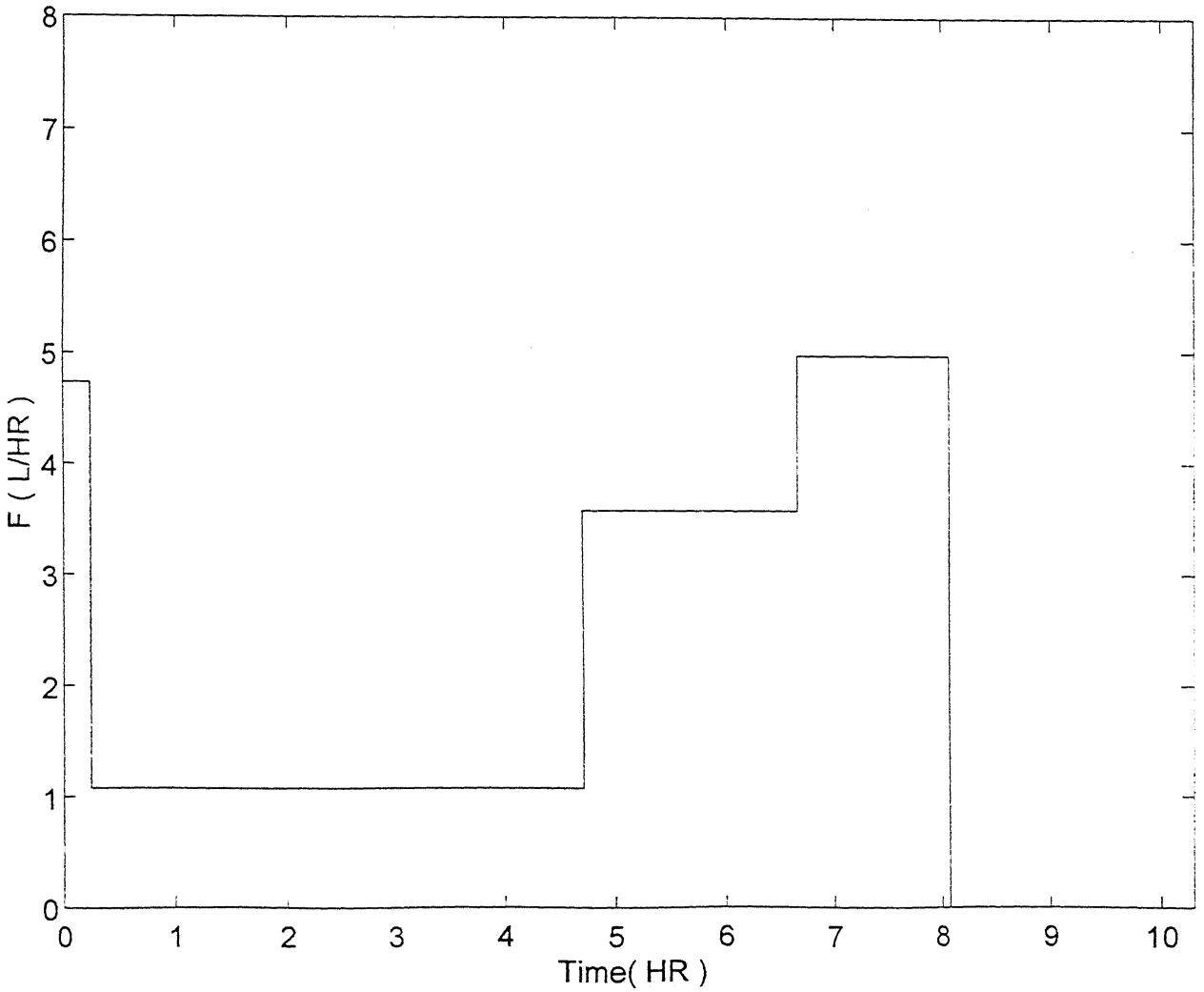


Fig12a The total optimisation problem using linear constraints U_{max}=7.0

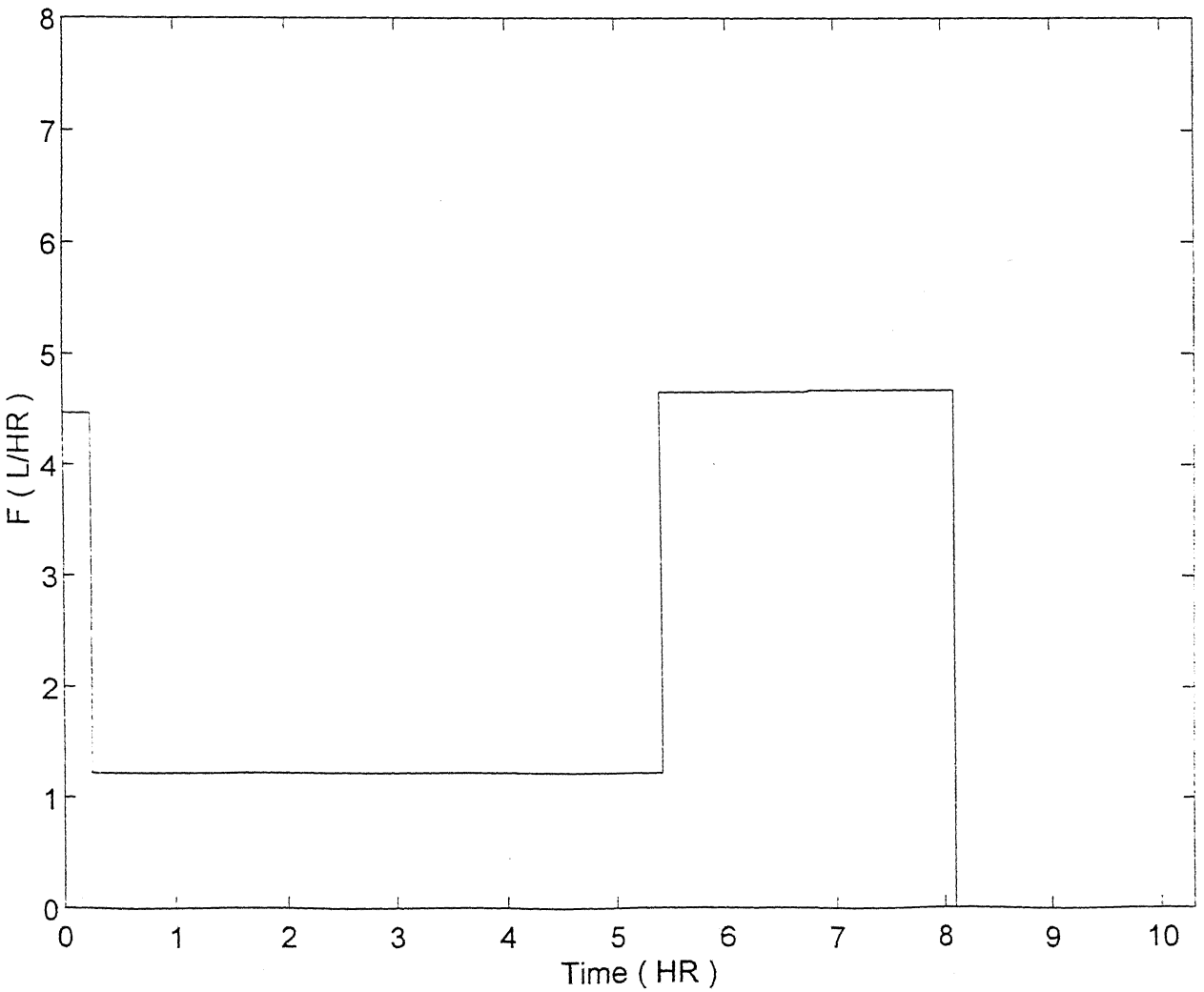


Fig12b The total optimisation problem using linear constraints U_{max}=6.3

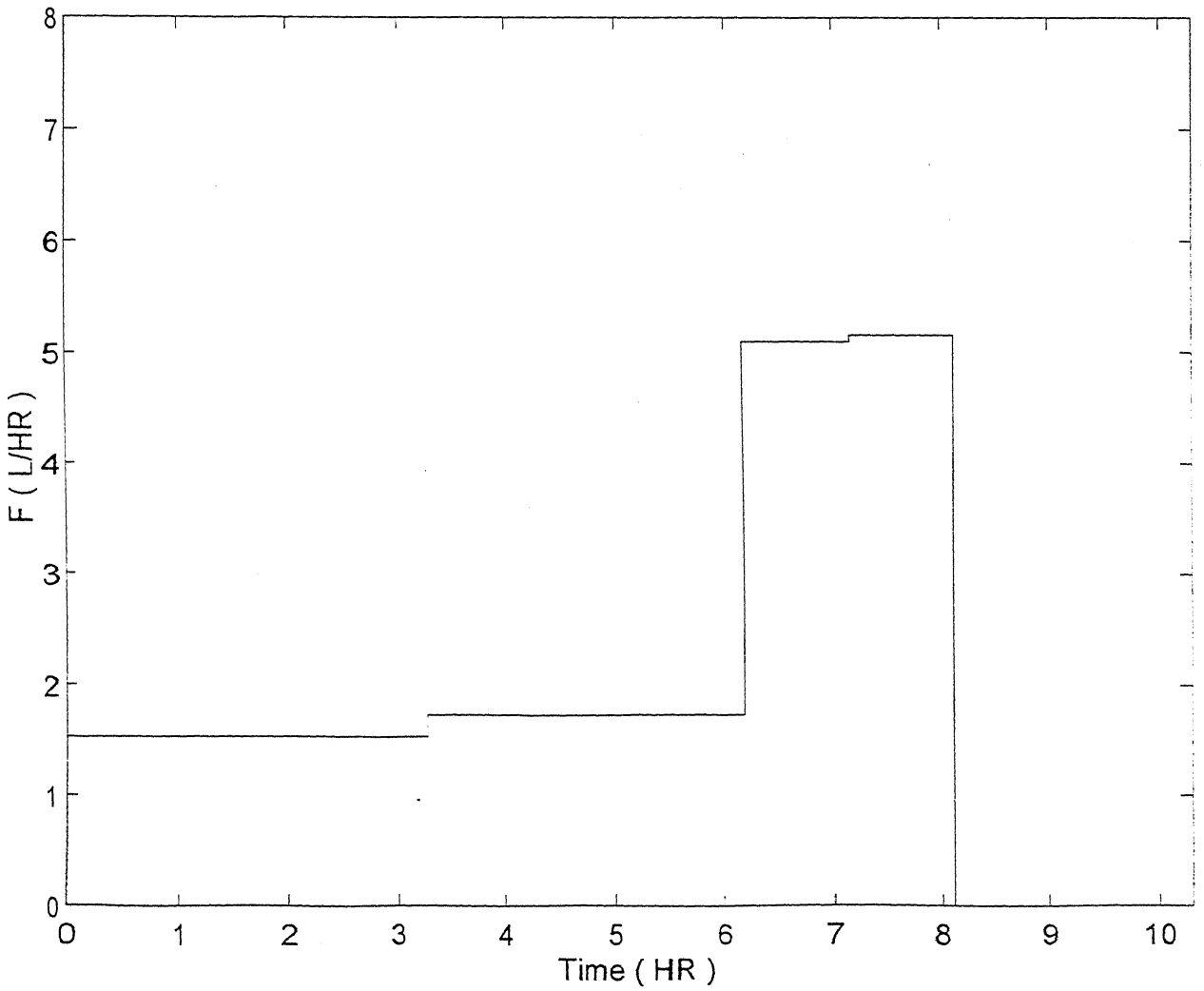


Fig.12c. The total optimisation problem using linear constraints U_{max}=5.0.

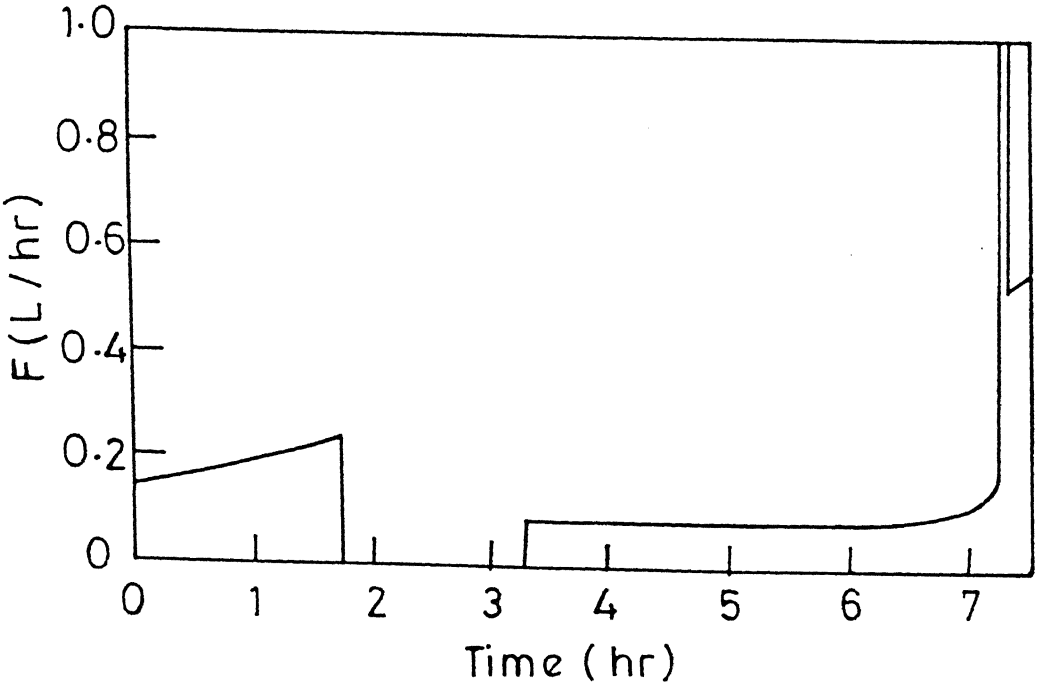


Fig13a Control profile obtained by Park and Ramirez
t_f=7.5

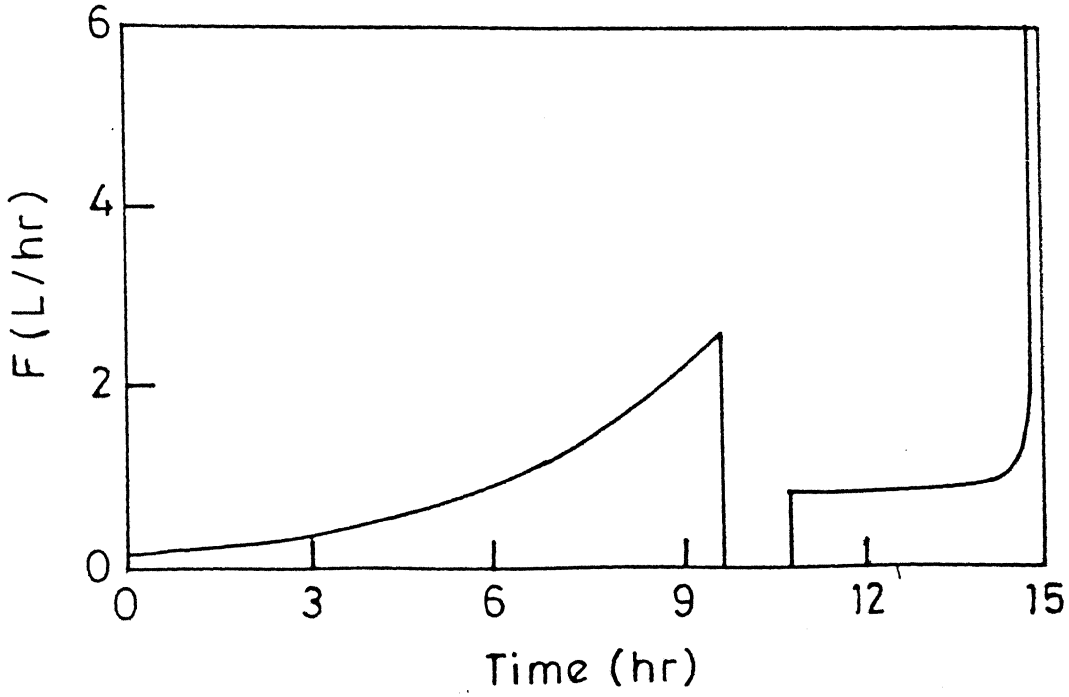


Fig13b Control profile obtained by Park and Ramirez
t_f=15

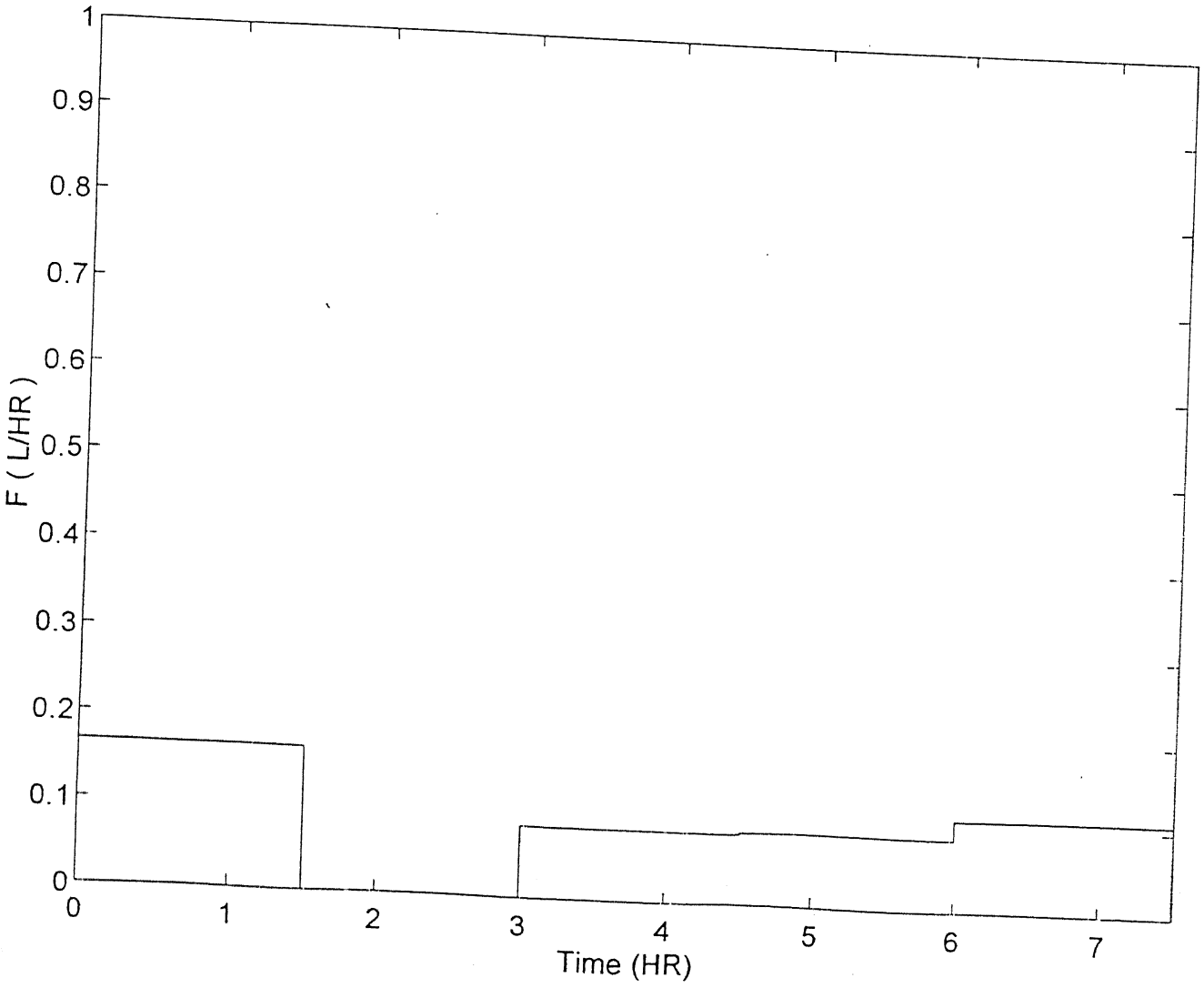


Fig14a Non-repeated fed batch, equal Δt's for t_f=7.5 hr. N=5

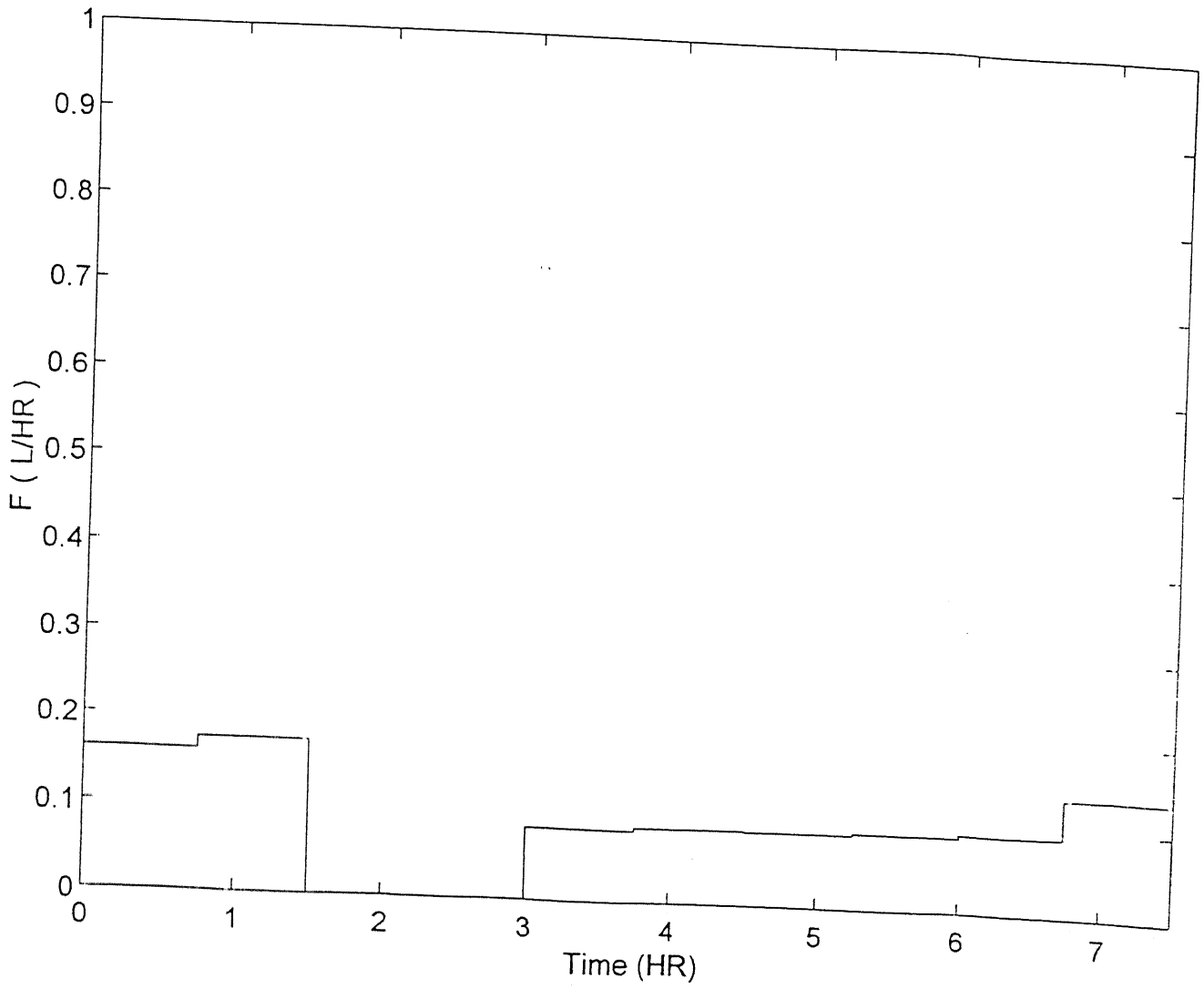


Fig14b Non-repeated fed batch, equal Δt's for t_f=7.5 hr. N=10

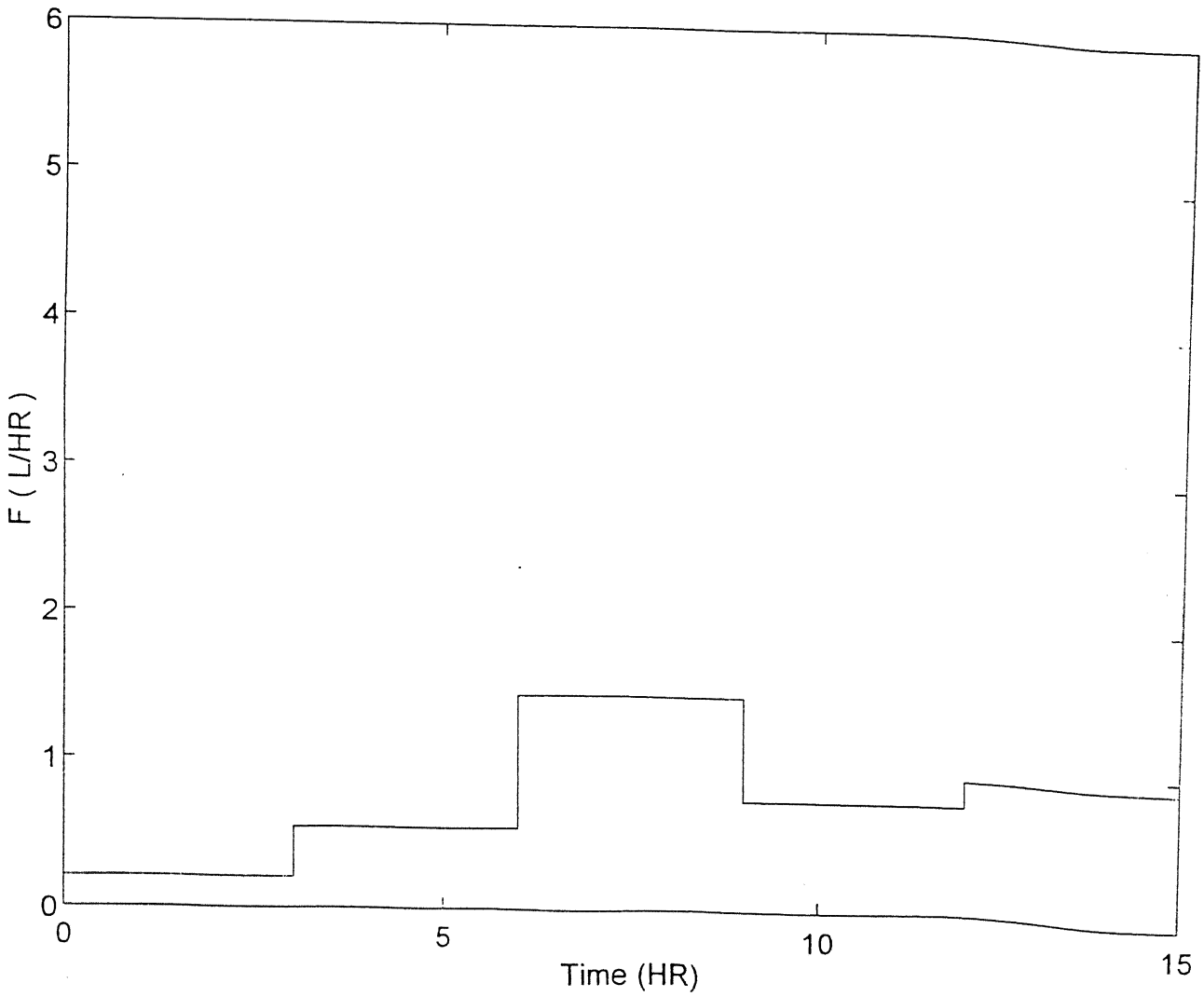


Fig15a Non-repeated fed batch ,equal $\Delta t^{\prime}s$ for t_f=15 hr. N=5

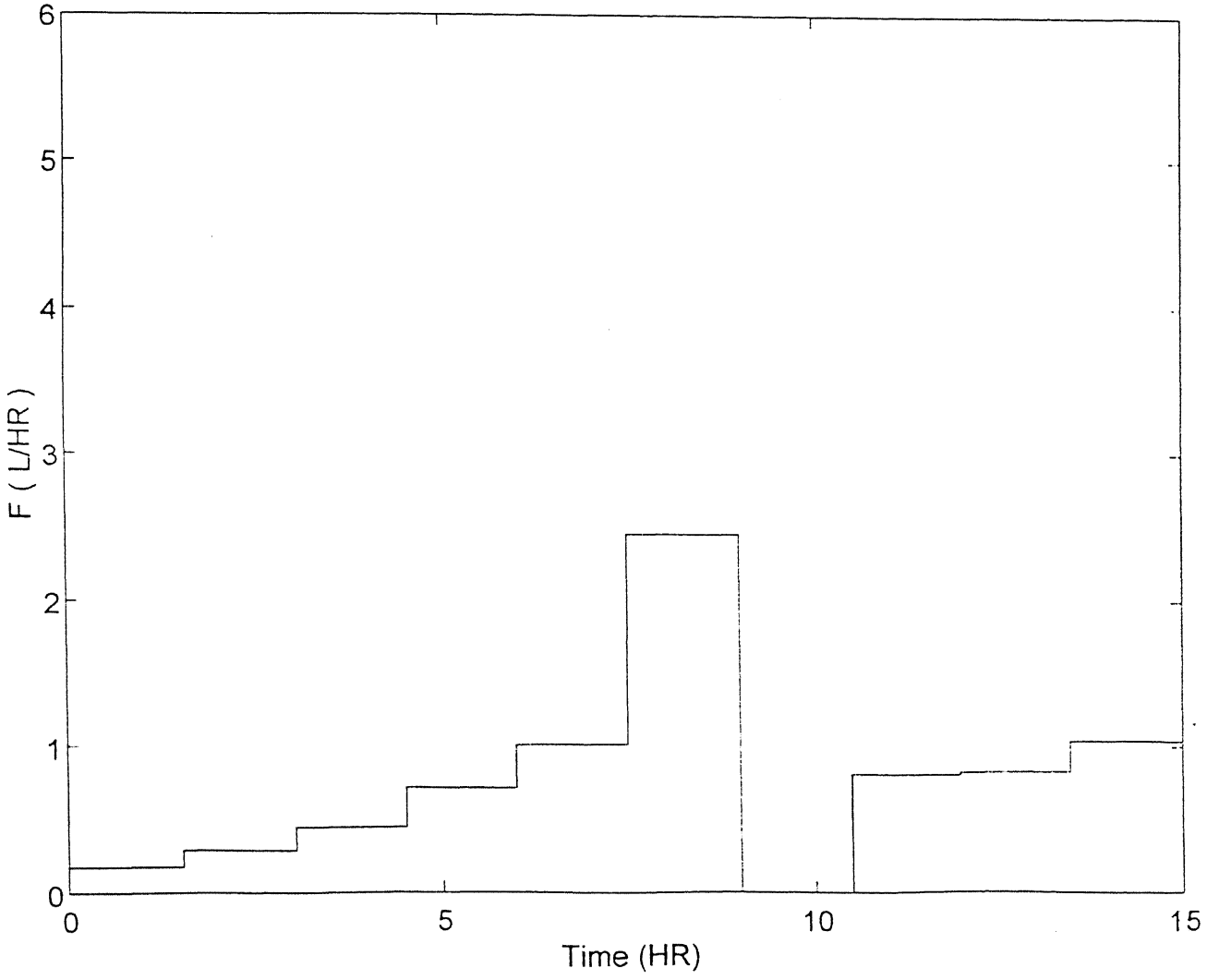


Fig15b Non-repeated fed batch ,equal Δt's for t_f=15 hr. N=10

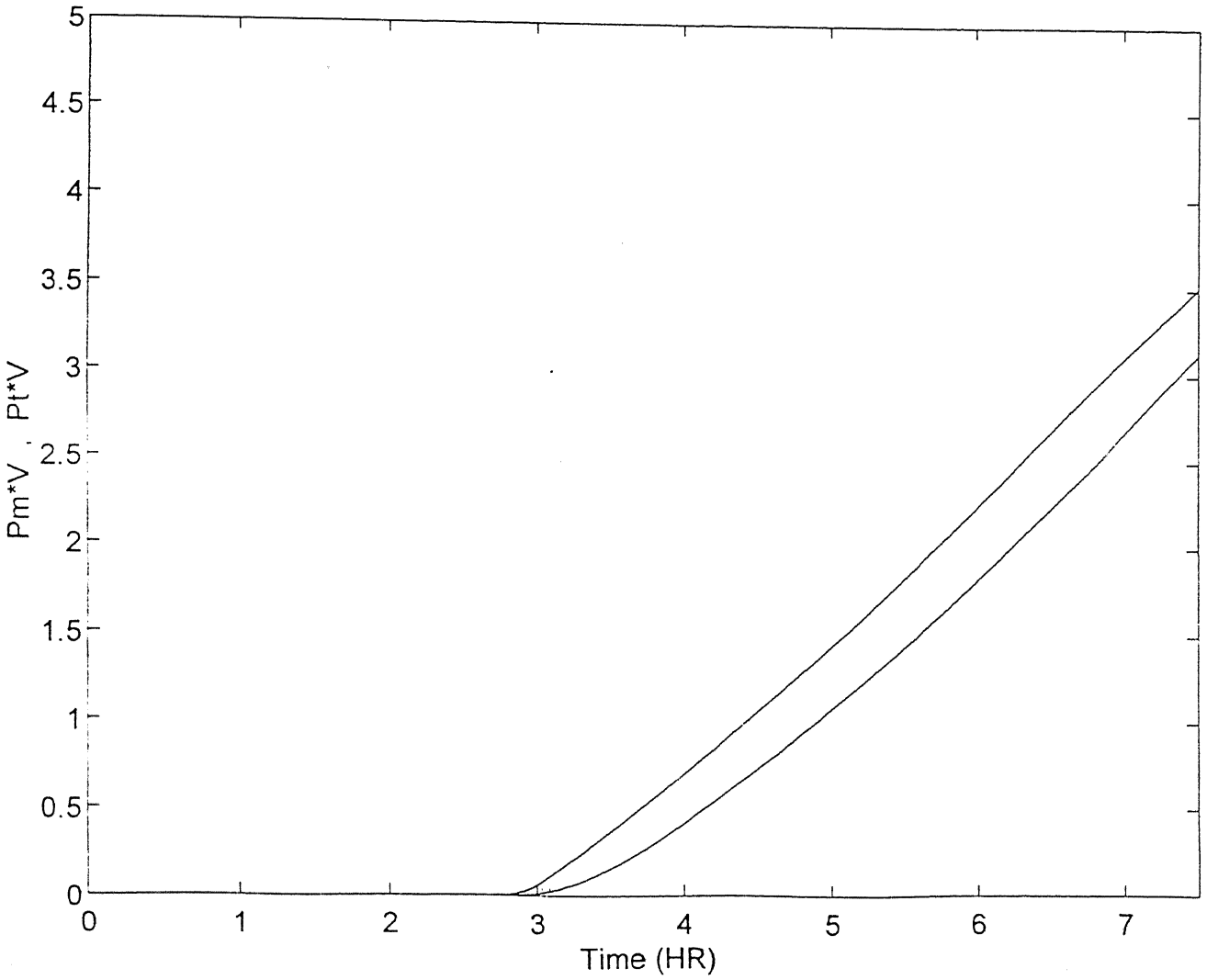


Fig16a $P_m V$, $P_T V$ for N=10 , t_f=7.5

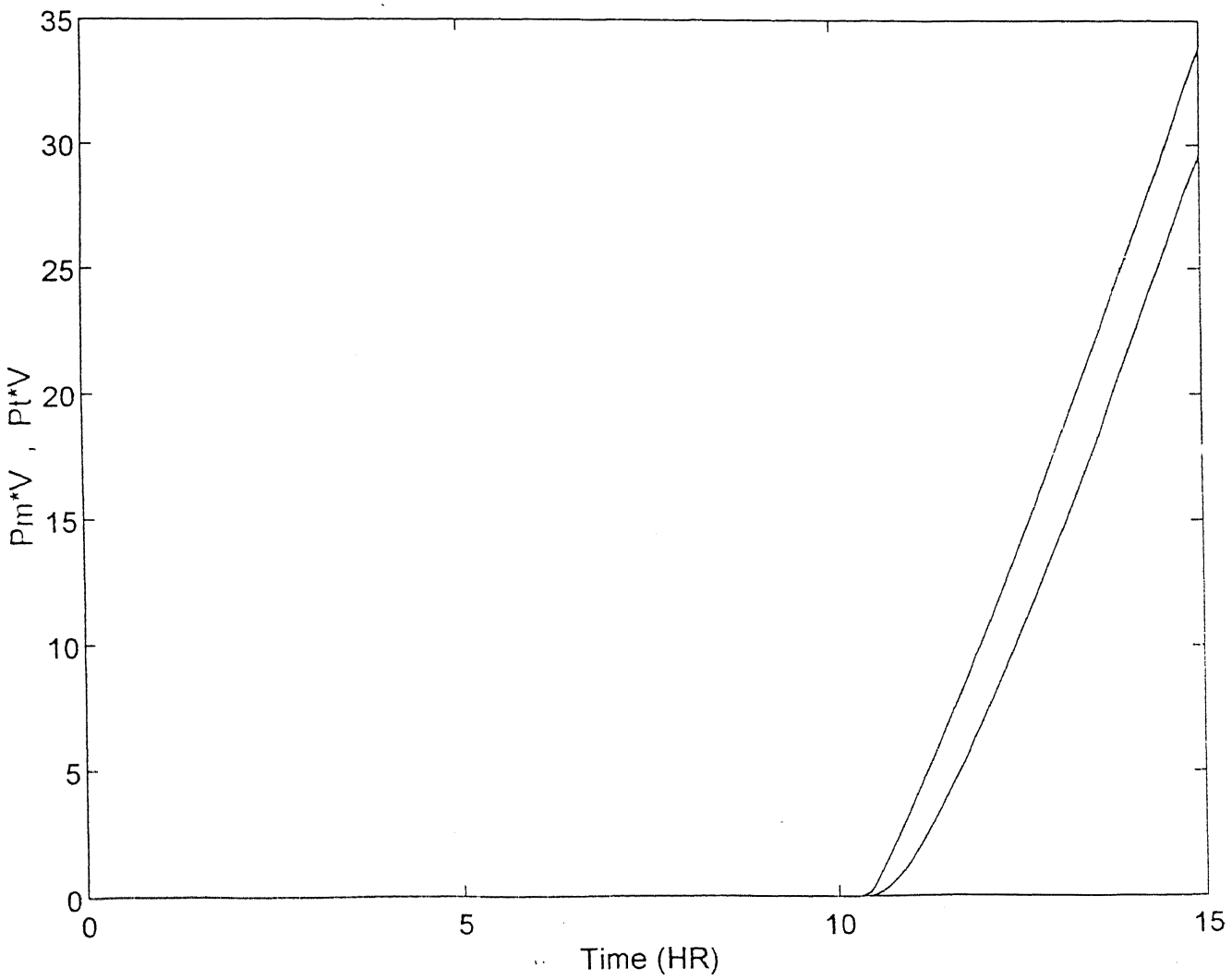


Fig16b $P_m V$, $P_T V$ for N=10 , t_f=15.0

Chapter 7

CONCLUSIONS

The use of the maximum principle to obtain solutions to optimal control problems is beset with many disadvantages. The optimal profiles are difficult to obtain theoretically in most cases. This is particularly the case when we have singular control. This is because the convergence on the solution using the adjoint equations is numerically difficult because of numerical instability.Once obtained these are difficult to implement experimentally.

We have shown how we can determine numerically the best strategy to maximise our objective function. This strategy can be obtained keeping in mind the constraints, which arise in the experimental implementation. Thus when we have flow-rates as the control variable we may be able to add instantaneously or at a constant value.

The advantage of the method proposed in this scheme here is it allows us to easily incorporate the effect of a finite value of an upper and lower bound on the control variable. More specifically it enables us to have the upper bound lower than the maximum value determined on the singular arc.

We have demonstrated how we can get the best possible approximations to the theoretical control profile obtained from Pontyagrin's maximum principle etc.

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Appendix-1

In this appendix we prove that the terminal state of RFB satisfies the stoichiometric relationship (2a).

Dividing (1a) by Y, multiplying (1c) by $(-S_F)$ and adding these to (1b) we obtain

$$\frac{d}{dt}\left(\frac{XV}{Y} + SV - VS_F\right) = 0$$

This equation is valid for each cycle .

The i^{th} cycle extends from t_o^i to t_f^i (Fig.1). To allow for discontinuities in the variables, the initial condition of X for the i^{th} cycle is denoted as $X(t_o^{i+})$ and the terminal condition as $X(t_f^{i-})$.

Clearly, then we have

$$V(t_o^{i+})\left(\frac{X(t_o^{i+})}{Y} + S(t_o^{i+}) - S_F\right) = V(t_f^{i-})\left(\frac{X(t_f^{i-})}{Y} + S(t_f^{i-}) - S_F\right)$$

Now $V(t_o^{i+}) = V_0$, $V(t_f^{i-}) = V_F$,

Defining $r = \frac{V_0}{V_F} < 1$

We obtain

$$\left(\frac{X}{Y} + S\right)\Big|_{t=t_o^{i+}} = r\left(\frac{X}{Y} + S\right)\Big|_{t=t_o^{(i+1)+}} + (1-r)S_F$$

Here we have made use of the fact that the concentrations are

continuous at the different stages. The terminal state at t_f^{i-} can be related to the initial state at $t_o^{(i+1)+}$, using this recursive relationship as

$$\left(\frac{X}{Y} + S\right)\Big|_{t=t_o^{n+}} = r^n\left(\frac{X}{Y} + S\right)\Big|_{t=t_o^{+}} + (1-r)(1+r+r^2\ldots+r^{n-1})S_F$$

Clearly, for $r < 1$, as $n \longrightarrow \infty$, $r^n \longrightarrow 0$ and we obtain

$$\left(\frac{X}{Y} + S\right)\Big|_{t=t_o^{n+}} = S_F$$

The initial concentrations in the terminal state of the RFB hence satisfy the stoichiometric relationship 2a.

Appendix-2

In this appendix we present the derivation of the singular arc.

If $H_F = 0$ for a finite time interval, say some $a \leq t \leq b$ and we cannot determine the value of F from $H_F = 0$, we will have singular control. To determine this, we get higher order time derivative of H_F and solve them simultaneously. In this case

$$\dot{H}_F = \frac{\lambda_X X^2 \mu'(X)}{V}$$

$$\ddot{H}_F = \lambda_X X^2 [-2F \mu'(X) + \mu'(X) V \mu'(X) - VX \mu'(X) - FX \mu''(X) + \mu(X) VX \mu''(X)] / V^2$$

On reduction of above two expressions, we get

$$\lambda_X \neq 0, \ \mu''(X) \neq 0, \ \mu'(X) = 0$$

$F = \mu(X)V$ and $\lambda_V - (X/V) \lambda_X = 0$

So we will have singular control only when $\mu'(X) = 0$. If we substitute this value of F in the state equation we get

$$\dot{X} = 0$$

$$\frac{dV}{dt} = \mu(X_i)V \text{ (where } X_i \text{ is the solution of } \mu'(X) = 0).$$

$$V = V(a) \exp(\mu(X_i))(t-a)$$

$$F = \mu(X_i) V(a) \exp.(\mu(X_i))(t-a)$$

Thus our total time of operation is divided into two parts:

(i) Time in filling the reactor t_{fill} along the singular arc

(ii) Time for batch operation t_{batch}.

and is given by

$$t_f = t_{fill} + t_{batch}$$

$$t_f = \frac{1}{\mu(X_i)} \ln\left(\frac{V_f\ X_i}{V_o\ X_f}\right) + \int_{X_i}^{X_f} \frac{dX}{X\ \mu(X)}$$

Appendix-3

In this appendix we show how the optimal control policy for N-pulses converges to the theoretical optimal policy for $N \longrightarrow \infty$. Expression for T_f in total optimisation problem for (N+1) pulses is given by

$$T_f = N \int_X^{rX} \frac{dX}{X\,\mu(X)} + \int_X^{X_f} \frac{dX}{X\,\mu(X)}$$

$$r = \left(\frac{V_f\, X}{V_o X_f} \right)^{1/N}$$

For the limiting case of $N \longrightarrow \infty$

We have

$$t_f = \lim_{N \longrightarrow \infty} \frac{\int_X^{rX} \frac{dX}{X\,\mu(X)}}{\frac{1}{N}} + \int_X^{X_f} \frac{dX}{X\,\mu(X)}$$

Using L-Ho'pital rule

$$t_f = \lim_{N \longrightarrow \infty} \frac{\left(\frac{V_f\, X}{V_o\, X_f} \right)^{1/N} \frac{1}{N^2} \ln \left(\frac{V_f\, X}{V_o\, X_f} \right)}{X \left(\frac{V_f\, X}{V_o\, X_f} \right)^{1/N} \mu \left(X \left(\frac{V_f\, X}{V_o\, X_f} \right)^{1/N} \right) \left(\frac{1}{N^2} \right)} + \int_X^{X_f} \frac{dX}{X\,\mu(X)}$$

For $N \longrightarrow \infty$

$$\left(\frac{V_f\ X}{V_o\ X_f}\right)^{1/N} = 1$$

$$t_f = \frac{1}{\mu(X)} \ln \frac{V_f\ X}{V_o\ X_f} + \int_X^{X_f} \frac{dX}{X\ \mu(X)}$$

This is identical to the expression of Weigand as derived in Appendix-2.

Now for t_f to be minimum for a fixed X_f

$$\frac{\partial t_f}{\partial X} = 0$$

This yields

$$\frac{\partial}{\partial X}\left(\frac{1}{\mu(X)}\right) = 0$$

where,

$X = \sqrt{\frac{\alpha}{\gamma}}$, in terms of the kinetic parameters in (12).